Antibiotic Use in a Cohort of Norwegian Children and Neonates Before, During and After Hospitalisation

Exploring focus areas for antibiotic stewardship

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Research environment

When the idea of this project occurred during 2016, I was working at the paediatric department at Ålesund Hospital in Møre og Romsdal Hospital Trust. From August 2018, I started working at the paediatric department at Haukeland University Hospital in Bergen. I was admitted to the PhD programme at the University of Bergen (Department of Clinical Science) and attached to the infection research group. I was also attached to the National Advisory Unit for Antibiotic Use in Hospitals at Haukeland University Hospital. Through my co-supervisors, The Norwegian Institute of Public Health, the University of Oslo and Oslo University Hospital have also been involved in the project on an institutional level.

Acknowledgements

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Abstract

Background: Appropriate antibiotic use in children is crucial in preventing antimicrobial resistance and to avoid disturbances of the microbiome.

Objectives: The aim was to develop an understanding of main aspects of antibiotic use pattern in Norwegian hospitalised children, both during hospitalisation, and before and after hospitalisation, and to identify focus areas for antibiotic stewardship.

Methods: We conducted period registrations of antibiotic use in 2017 in a district hospital and in a university hospital. The cohort of children from the district hospital was linked to the Norwegian Prescription Registry; ambulatory antibiotic use in these children were collected one year before and one year after hospitalisation. Through the Norwegian Population Registry, we established a matched reference group.

Results: For children after the neonatal period (N=238), we found that total adherence rate to the antibiotic guideline was 72%, and 21% of treatments involved broad-spectrum antibiotics, whereof 68% were given to children with comorbidities. We found wide differences in dosing within and between the hospitals, and in the proportion of treatments for pneumonia. For neonates (N=184), we found that 82% of 121 treatments for suspected early-onset sepsis in those with gestational age of at least 28 weeks were given for unconfirmed infections, with an average treatment length of 3.1 days. In children more than three months, the relative risk of antibiotic exposure before hospitalisation was 2.9 (95% confidence interval 2.4-3.5) during the year before hospitalisation and 2.8 (2.3-3.3) during the year after hospitalisation compared to the reference group. In infants less than three months, the relative risk of antibiotic exposure was 1.7 (1.1-2.5) during the year after hospitalisation compared to the reference group. Comorbidity adjustment led to a slightly lower relative risk.

Conclusions and implications: We found areas requiring further attention, such as the high proportion of unconfirmed infections in neonates, use of broad-spectrum antibiotics in children with comorbidities, treatments for pneumonia and antibiotic dosing. Both children and infants who had received antibiotics in-hospital had higher risk of receiving antibiotics in ambulatory care, an aspect that should be considered when monitoring antibiotic use in the future.

Sammendrag

Bakgrunn: Rasjonell antibiotikabruk blant barn er essensielt for å unngå økende antibiotikaresistens samt forstyrrelser i deres normale bakterieflora.

Formål: Hensikten med dette prosjektet var å tilegne oss en bedre forståelse av mønster i antibiotikabruk blant norske barn innlagt i sykehus, både under innleggelsen, samt før og etter innleggelsen. Vi ønsket gjennom dette finne fokusområder for framtidig antibiotikastyring for barnepopulasjonen.

Metode: Vi gjennomførte registreringer av antibiotikabruk i 2017 ved et distriktssykehus og et universitetssykehus. Kohorten av barn fra distriktssykehuset ble koblet mot Reseptregisteret og vi registrerte utleverte antibiotikaresepter et år før og et år etter innleggelsen. Gjennom Folkeregisteret etablerte vi en matchet kontrollgruppe.

Resultater: For barn etter nyfødtperioden (N=238) fant vi at etterlevelsen av retningslinjene for antibiotikabruk var 72%, og at 21% av behandlingene involverte bredspektret antibiotika, hvorav 68% ble gitt til barn med komorbid sykdom. Vi fant store forskjeller i dosering innad og mellom sykehusene, samt i andel behandlinger som ble gitt for lungebetennelse. For nyfødte (N=184) fant vi at 82% av 121 behandlinger mot mistenkt tidlig sepsis blant de med gestasjonsalder på minst 28 uker ble gitt mot ubekreftede infeksjoner med en gjennomsnittlig behandlingslengde på 3.1 dager. Hos barn eldre enn tre måneder fant vi en relativ risiko for antibiotika-eksponering på 2.9 (95% konfidensintervall 2.4-3.5) gjennom året før sykehus-innleggelsen og 2.8 (2.3-3.3) året etter sykehusinnleggelsen, sammenlignet med kontrollgruppen. Hos spedbarn yngre enn tre måneder fant vi en relativ risiko for antibiotikaeksponering på 1.7 (1.1-2.5) gjennom året etter sykehusinnleggelsen, sammenlignet med kontrollgruppen. Komorbiditets-justering førte til noe lavere relativ risiko i alle analysene.

Konklusjon og fortolkning: Vi avdekket områder som krever videre oppmerksomhet slik som den høye andelen av ubekreftede infeksjoner blant nyfødte, bruk av bredspektret antibiotika blant barn med komorbid sykdom, behandling av lungebetennelse og dosering av antibiotika. Både barn og spedbarn som hadde fått antibiotika i sykehus hadde høyere risiko for å få resept utenfor sykehus.

List of publications

1. Thaulow CM, Blix HS, Eriksen BH, Ask I, Myklebust TÅ and Berild D. Using a period incidence survey to compare antibiotic use in children between a university hospital and a district hospital in a country with low antimicrobial resistance: a prospective observational study. *BMJ Open.* 2022: 9;e027836. doi: 10.1136/bmjopen-2018-027836

2. Thaulow CM, Berild D, Blix HS, Brigtsen AK, Myklebust TÅ and Eriksen BH. Can We Optimize Antibiotic Use in Norwegian Neonates? A Prospective Comparison Between a University Hospital and a District Hospital. *Front. Pediatr.* 2019; 7:440. doi: 10.3389/fped.2019.00440

3. Thaulow CM, Blix HS, Nilsen RM, Eriksen BH, Wathne JS, Berild D, Harthug S. Antibiotic use in children before, during and after hospitalisation. *Pharmacoepidemiol Drug Saf.* 2022; 31(7): 749-757. doi:10.1002/pds.5438

4. Thaulow CM, Harthug S, Nilsen RM, Eriksen BH, Wathne JS, Berild D, Blix HS. Are infants exposed to antimicrobials during the first 3 months of life at increased risk of recurrent use? An explorative data-linkage study. *Journal of Antimicrobial Chemotherapy.* 2022; 77(5): 1468–1475. https://doi.org/10.1093/jac/dkac024

For all articles, the reuse for the purpose of this thesis was permitted

Abbreviations

AB+, Infants who had received antibiotics during the first three months of life

AB-, Infants who had not received antibiotics during the first three months of life

AMR, Antimicrobial resistance

BSA, Broad-spectrum antibiotics

CF, Cystic fibrosis

CI, Confidence interval

CNS, Central nervous system

CI, Confidence interval

CRP, C-reactive protein

DH, District hospital (Ålesund hospital)

ECMO, Extracorporeal Membrane Oxygenation

EOS, Early-onset sepsis

GA, Gestational age

H+, Children who had received antibiotics during hospitalisation

H-, Children who had not received antibiotics during hospitalisation

IQR, Interquartile range

IRR, Incidence rate ratio

IV, Intravenous

LOS, Late-onset sepsis

NICU, Neonatal intensive care unit

WHO, World Health Organization

NORM, Norwegian Surveillance System of Antimicrobial Resistance

NorPD, Norwegian Prescription Registry

PPS, Point prevalence survey

RR, Relative risk

SD, Standard deviation

1. Introduction

1.1 Antibiotic use and resistance – history and global context

The invention and development of modern antibacterial drugs (antibiotics) started with the discovery of penicillin in 1928 by Alexander Fleming, a microbiologist at St. Mary`s Hospital in London. Penicillin was discovered accidently as a zone inhibiting bacterial growth around an invading fungus on an agar plate [1]. During the 1940`s, penicillin was introduced as a therapeutic drug. This marked a scientific revolution within medicine history. Following the discovery of penicillin, numerous of novel classes of antibiotics were discovered, acting on different types of bacteria. An efficient treatment was established for bacterial infections that previously had killed millions of people.

Shortly after the post-antibiotic era had started, one detected that widely use of these drugs led to increasing number of resistant bacterial strains that inhibited the therapeutic effect of antibiotics. For example, in 1937, sulfonamides were introduced as another class of antibiotics, but resistant strains were detected shortly after [2]. From 1960, the development of antimicrobial resistance (AMR) accelerated [2]. The first studies monitoring antibiotic use in humans in order to limit its use and slow down resistance, was published already in the 1960-1970s [3, 4]. The term antibiotic stewardship was introduced in 1996 and has since then been used in relation to interventions, programs and surveillance aiming to optimize the use of antibiotics in humans [5-7]. Also, the challenge of too much antibiotic use in animals and agriculture was set on the agenda in 1968 [8]. However, it is first during the last decade that the threat of AMR has been properly highlighted at the governmental level as a large scaled global health crisis in need of urgent multifaceted global solutions [9]. In this thesis, we focus on antibiotic use in humans.

According to the World Health Organization (WHO), AMR is one of the greatest treats to global public health [9]. The development of AMR is closely related to

superfluous and inappropriate use of antibiotics [9-11]. Concomitant with the world-wide increase in AMR, there is a lack of novel antibiotics in the pipelines of the pharmaceutical companies (Figure 1) [12, 13]. Murray et.al estimated that 1.27 million deaths in 2019 were directly consequences of AMR [14]. In the upcoming years, AMR can lead to a further increase in mortality caused by common infections, increased costs, and it can threaten modern medicine like cancer treatment and transplantations. However, to estimate the exact impact of AMR in the future is difficult and uncertain.[15, 16] To preserve antibiotics as useful drugs, it is essential to monitor antibiotic consumption, understand patterns of use and aim to optimize the use of the existing antibiotics and minimize the use of broad-spectrum antibiotics as these affect many bacteria and are particular active in trigging resistance. More prudent use of antibiotics may inhibit further increasing AMR rates and even lead to decreasing AMR rates as exemplified by ciprofloxacin; resistance rate increased almost parallel to increased use, but has decreased the last years after more strict use (Figure 2) [17]. Importantly, even if novel antibiotics are discovered, the challenge of AMR will remain, and focus on improved and rational use of antibiotics (antibiotic stewardship) will remain a cornerstone in keeping the efficiency of these valuable medicines.
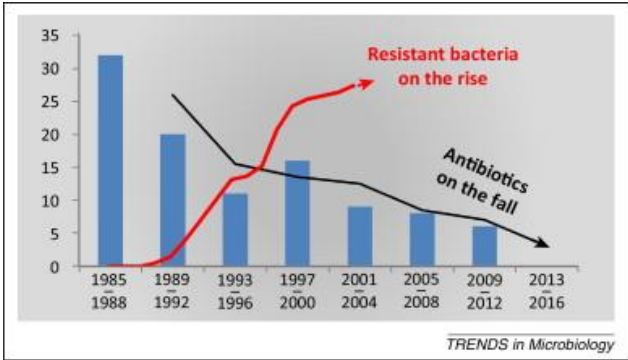
Figure 1. Illustrating the rise of AMR and the lack of new antibiotics. The blue bars show the number of novel antibiotics launched in the different time-periods. The red line shows the percentage of resistance to vancomycin in US intensive care units. The black line indicates the average trend of novel antibiotics introduced [12]
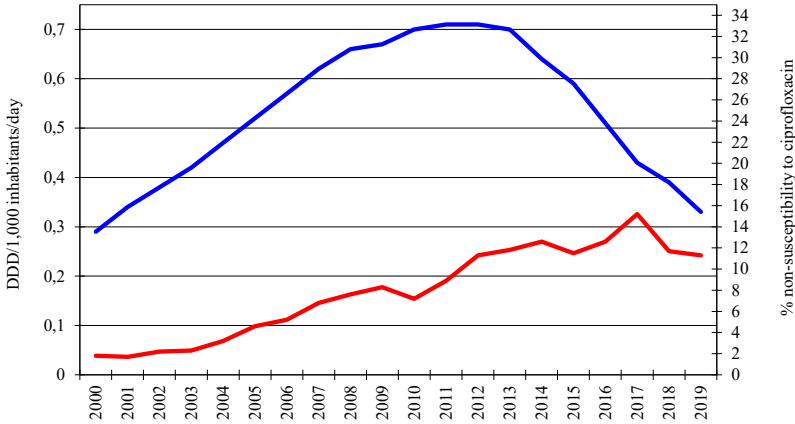
Figure 2. Usage of ciprofloxacin (blue) and prevalence of ciprofloxacin resistance in *Escherichia coli* blood culture isolates in Norway (red) [17]

1.2 Antibiotic use and antimicrobial resistance in Norway

In Norway, The Norwegian Surveillance System of Antimicrobial Resistance (NORM) has surveilled antibiotic use and antimicrobial resistance nationally since year 2000. Compared to other countries, the prevalence of AMR in Norway is low and narrow-spectrum antibiotics can still be used for most indications [18-20]. In spite of low resistance rates, use of BSA in Norwegian hospitals increased gradually until 2012 [18]. At that time, the Norwegian Government launched a National Strategy against AMR that included a 30% reduction of total antibiotic use by 2020 and a 30% reduction in the use of broad-spectrum antibiotics (BSA) in hospitals [21]. These BSA are defined as second- and third-generation cephalosporines, carbapenems, piperazillin-tazobactam and quinolones. In this thesis, we have used this definition and also included prescriptions of 4th and 5th generation cephalosporins. Hereafter, the abbreviation BSA is used for these specific antibiotics, while broad-spectrum antibiotics is used when not referring to specific antibiotics.

Since 2012, the BSA use in hospitals has decreased by approximately 15% [18]. In 2017, Holen et al concluded that the use of BSA in Norwegian hospitals (entire population) can be reduced [22]. Importantly, reports from NORM mainly present aggregated hospital-data for the entire population, and detailed data on the paediatric population is missing.

1.3 Children and their vulnerability to antibiotic exposure

Until recently, the global trend of increasing resistance to antibiotics in children and neonates particularly, has received relatively low attention [23]. Also, young children have a microbiome that is under development that gradually matures towards an adult-like microbiome during the first years of life. This process is also linked together with the developing immune and metabolic system [24]. Exposure to antibiotics in this period can lead to antimicrobial resistance [25, 26], but it can also cause unfavorable disturbances

in the developing process of the microbiome [27-29]. Several studies have shown a connection between antibiotic exposure in childhood and an increased risk of numerous medical conditions such as obesity, asthma, allergy, atopic dermatitis, intestinal bowel disease, celiac disease, impaired growth and Attention Deficit Hyperactivity Disorder [28-35]. Moreover, one study also concluded that neurocognitive behavior could be altered by infantile antibiotic use [36]. In premature infants, antibiotic use has been associated with increased mortality and morbidity [37, 38] Thus, rational use of antibiotics in children, and especially the youngest children, is of utmost importance.

1.4 Antibiotic use in children (after the neonatal period)

Ambulatory antibiotic use in children is reported from various settings worldwide aiming to monitor use and target areas for improvement [39-46]. One study showed that children in Norway received less antibiotics and less broad-spectrum antibiotics than children in Hungary and Portugal [39]. Another study showed that antibiotic consumption in Norwegian ambulatory care also was low compared to Germany, the USA, Italy, Spain and South-Korea [46]. A registry-based nationwide study revealed a 24% reduction in ambulatory antibiotic use in Norwegian children 0-17 years from 2012 to 2016, but found great geographical variance in use, and concluded that antibiotic consumption could be further reduced [47]. Data from NORM showed a 33% reduction in ambulatory antibiotic use for children 0-9 years between 2012 and 2019 [18].

Ambulatory antibiotic use in Norway can easily by surveyed through the Norwegian Prescription Database (NorPD) [48]. However, surveilling inpatient antibiotic use in Norwegian children is more challenging. Data are most often based on crude antibiotic sales from the hospital pharmacy and presented as Defined Daily Dose, a technical unit based on an adult`s average weight (70 kg) [18]. Thus, the WHO recommend using

the prescribed daily dose when analyzing paediatric inpatient antibiotic use [49], exemplified by Porta et al. in 2012 [50]. This requires individual patient data and is more demanding to achieve. Worldwide, point-prevalence surveys (PPS) have been used as a tool to monitor inpatient antibiotic use in children, both within countries [51-54] and in large global cross-country surveys [55, 56]. These studies have used individual patient data, but the observations have mostly been limited to one single day. Global studies have shown wide differences in antibiotic use pattern between and within countries [50-56].

Respiratory tract infections are reported to be the most common indication for antibiotic treatment in hospitalised children [50, 52, 55, 56]. Underlying medical conditions have been observed in 25-56% of paediatric inpatients receiving antibiotics [50, 52]. A low adherence rate to antibiotic guidelines is a challenge in many settings, specifically in lower respiratory tract infections.[57-59] Moreover, finding an agreement regarding the optimal antibiotic dose for children in relation to body mass has been challenging [50, 60-64]. One study concluded that understanding the competition pattern between resistant and sensitive pathogens in a host is crucial to decide whether a higher or lower dose of antibiotics should be administered to keep antibiotic resistance low [65]. The mutant selection window theory purposes that high enough doses is important [66]. In clinical practice, the most important challenge is variation between guidelines and that suggested dose intervals for many indications are wide [64]. Thus, different interpretations may be a problem. Information on dosing practice in Norwegian hospitalised children is lacking.

Data on antibiotic use in Norwegian hospitalised children was limited and outdated before our research group started this project. Berild et al. conducted an interventional study between 1994 and 1996 in one single paediatric department in Oslo, and showed that antibiotic use could be halved without compromising the quality of patient care [67]. From 2003-2005, Senstad et al. collected data on cases of community-acquired pneumonia in children from another hospital in Oslo. The authors found that penicillin was used as an effective treatment in close to all cases [68]. Raastad et al. revealed

increased consumption of BSA in a highly specialized paediatric department in Oslo from 2002 to 2009 [69]. A student thesis from the University Hospital of North Norway described antibiotics used in the treatment of urinary tract infections in children from 2007 to 2016 [70]. In 2019, our research group published national data on antibiotic use in children [54]. We found that approximately one out of four hospitalised children in Norway were given antibiotics, whereof one third received BSA. The study also showed that adherence to antibiotic guidelines was low (48%). These data were based on quarterwise one-day PPS conducted between 2013 and 2017. The data lacked information on comorbidities, duration of treatment, microbiological results and doses of antibiotics. Thus, we regarded that these national data needed to be supplemented with more detailed data surveilling antibiotic use for a longer continuous time-period.

An unexplored field is the association between being hospitalised for antibiotic treatment and the potential risk of getting more antibiotics in ambulatory care after discharge. Antibiotic stewardship interventions have been proposed especially for patients with recurrent antibiotic use [71]. However, the link between ambulatory and in-hospital antibiotic use is not well studied as consumption pattern during hospitalisation and in ambulatory care most often are reported separately using different data sources. Lipsett et al. reported that children in ambulatory care treated with antibiotics with broader spectrum had increased risk of hospitalisation compared to those being treated with antibiotics with narrower spectrum, even after adjusting for clinical severity measures [72]. A study in adults revealed an excess of antibiotic use after discharge from hospital [73], and a study in children showed inappropriate antibiotic prescriptions given at discharge in cases of urinary tract infections [74].

Antibiotic exposure in-hospital could include complicated infections with resistant bacteria and long-lasting infection morbidities [75]. Additionally, psychological and behavioural factors in parents and prescribers could be of importance in antibiotic prescribing decisions [76-78]; hospitalisations could cause increased concern from parents lowering the future threshold to seek medical help, potentially increasing the number of antibiotic prescriptions. In contrast, an event of hospitalisation could be followed by

accurate diagnostic work-up, targeted treatments, and follow-up from specialist care. We wondered if and how antibiotic exposure to hospitalised children was associated with their antibiotic consumption pattern in ambulatory care.

1.4 Antibiotic use in neonates

Neonates and small infants have the most immature microbiome and are particularly vulnerable to antibiotic exposure [27, 29-32]. On the other hand, compared to other age groups, the incidence of severe bacterial infections including sepsis is considerable [79, 80]. Thus, antibiotic exposure rates are high; a registry-based study from Norway (2009-2011) found that 2.3% of all live born term infants were exposed to antibiotics within the first week of life. Of these, only 2.3% were culture-confirmed cases and 54% were not diagnosed with a bacterial infection [81]. International reports have also demonstrated the potential for reduced antibiotic use in neonates [82-84]. Use of BSA is low in neonates compared to older children [54, 55], but empirical treatment for sepsis varies; namely whether to use ampicillin or penicillin in combination with an aminoglycoside [54, 55, 85]. Furthermore, there is a lack of studies and consensus in neonatal antibiotic dose regimes [86].

Evaluating risk factors, clinical symptoms and biomarkers in neonates can be challenging, reflected by variation in antibiotic exposure rates between hospitals, also within the same countries [81, 84]. In Norway, a maximum c-reactive protein (CRP) value of more than 30 mg/L is required for the diagnosis of a culture-negative neonatal sepsis [87], but to our knowledge no studies from Norway have included CRP values when reporting and analysing antibiotic use in neonates after this criteria were invented.

After the early infancy (first three months of life), the incidence of invasive bacterial infections decreases [79]. Despite this, data from various countries suggests that antibiotic prescribing practice could be more rational also in late infancy, especially in

respiratory tract infections [45, 88]. In Norway, one out of five children up to the age of four were prescribed an antibiotic in ambulatory care in 2017 [48]. While infants less than three months, as a rule of thumb, are admitted to hospital for intravenous (IV) antibiotics, older infants more often get oral ambulatory prescriptions.

There is little knowledge of recurrent antibiotic prescriptions in infants. A complete picture of this topic would require data from both the hospital setting and ambulatory care. This is important, as recurrent antibiotic use in infancy might be an even stronger risk factor for developing chronical medical diseases [32-34]. Infants with infection-related comorbidities are suspected to have increased risk for subsequent antibiotic use; an example is recurrent pyelonephritis [89]. However, early-life antibiotic exposure could also give AMR or alterations in the microbiome, possibly interacting with the immature immune system. This could alter the rate and presentation of infections and the antimicrobial consumption pattern. Previous studies have also reported that behavioural, psychological and socioeconomic factors could be of importance when evaluating antibiotic use [45, 76-78, 90, 91]. After an event of antibiotic exposure shortly after birth, several psychological aspects could be of importance; more careful behaviour in society decreasing the risk of catching infectious symptoms; increased worry among parents lowering the threshold for seeking medical help; expectations from parents that antibiotics would be beneficial; behaviour among prescribers that could be influenced by previously use of antibiotics. Summing all these considerations up, we hypothesized that antibiotic exposure shortly after birth would lead to an increased risk of recurrent antibiotic use.

1.5 Paediatric care in Norway

In Norway, there are 64 hospitals registered on a public available list [92]; six of these are university hospitals, while the others are district hospitals or hospitals with specific functions. All acute medical care in Norway is provided in public hospitals. There are twenty-two paediatric departments in Norway with acute functions and 20 neonatal

units. Fifteen of the neonatal units provide prolonged intensive care such as mechanical ventilation support [93]. The general upper age limit for paediatric departments in Norway is 18 years. A large proportion of the paediatric population have a long travel distance to their closest hospital, especially in the more rural parts of Norway. Most paediatric departments include all children, also those with surgical conditions. Comparing antibiotic use in hospitals with different sizes and academic cultures is important to get a valid description of antibiotic prescriptions throughout the country. Most of the academic environment including scientific positions and student teaching are situated at university hospitals. Thus, these hospitals are expected to be at the forefront of implementing new knowledge. We wanted to investigate whether there is any clear differences in antibiotic use practice in children between university and district hospitals.

1.6 Antibiotic guidelines in Norway

In Norway, the Directorate of Health have published national guidelines on empirical recommendations for antibiotic treatments for various indications both for primary care and for hospitals. However, the guidelines for hospitals are only valid for children > 12 years of age. The Norwegian Paediatric Association have published a commonly used guideline (hereafter called the Guideline) for acute and general paediatrics, including empirical antibiotic recommendations for most indications [87]. For neonates, the University Hospital of North Norway have made an educational book for neonatal medicine that also includes antibiotic recommendations; this book has been revised recently and is now included as part of the Guideline. In general, penicillin is emphasized for most respiratory tract infections. In children after the neonatal period, ampicillin plus an aminoglycoside is recommended for suspected sepsis, neutropenic fever and for IV treatment of pyelonephritis. In neonates, penicillin plus an aminoglycoside is recommended for suspected early-onset sepsis (EOS) while cephalexin plus an aminoglycoside is recommended for late-onset sepsis (LOS). For suspected infections in the central nervous system (CNS), a third-generation

cephalosporin is recommended; it is the only indication where BSA are recommended empirically. For infections in skin, soft-tissue, bone and joint, the Guideline recommends cloxacillin, penicillin, cefalotin or clindamycin for IV treatments, alone or in combination.

1.7 Knowledge-gap

Together with my supervisors, I identified an urgent need for detailed descriptions of paediatric antibiotic use in Norwegian hospitals, and I regarded that it would be important to achieve information from different parts of the country and in both district and university hospitals. Furthermore, I also identified a knowledge gap in the relation between in-hospital and ambulatory antibiotic consumption that I aimed to investigate.

1.8 Literature search

We searched Medline, Embase and Pubmed for relevant literature combining different keywords and Medical Subject Headings (MeSH) according to the different parts and aims of our project (Table 1) References were critically reviewed for their appropriateness in relation our project. The last search was performed 5th of February 2022.

Examples of specific search strategies from Medline using no limitations in time-range and inclusion of words in abstract, title or as keyword: ("antibacterial" OR "antibiotic" OR "antimicrobial") AND ("use" OR "prescri*" OR "consumption") AND ("child*" OR "paediatric" OR "pediatric" OR "infant*" OR "neonat*") AND ("hospital" OR "inpatient" OR "department" OR "unit") AND ("Norway" OR Norwegian*). This search gave 80 results. When removing Norway OR Norwegian* 20942 studies were found. To target follow up studies combining data on antibiotic use in hospital and in

ambulatory care we added ("primary care" OR "ambulatory care" OR "outpatient") to the search and 169 studies were found. We also did further searches targeting follow up-studies of antibiotic use in hospitalised children including words such as "recurrent", "repeated", "follow-up" and "risk" In relevant articles, we reviewed the reference lists for additional studies of interests.

	ELEMENT 1	ELEMENT 2	ELEMENT 3	ELEMENT 4	ELEMENT 5	ELEMENT 6
Search word	Antibiotics	Use of	Children	Hospital	Primary care	Others
Free text Title/ Abstract	Antibiot* Antibacter* Antimicrobi* Penicillin*	Use Survey surveillance exposure Prescrib* Prescript* consumption	Child Children Paediatric* Pediatric* Infant Neonat* Premature Preterm	Hospital* Inpatient	Outpatient Ambulatory care Primary health care Family doctor Family physician	Broad-spectrum antibiot* Adherence Compliance Guideline* Recurrent Repeated Dose Comparative Comparison Difference
Medical Subject Headings	Antibacterial agents	Drug Prescriptions Antimicrobial Stewardship	Child Infant	Hospital Hospitalisation Hospitalised Child	Ambulatory Care Physicians Primary health care	Scandinavia Norway

Table 1. Overview of words and Medical Subject Headings (MeSH) used in the literature search for this project

2. Objectives

The all-over aim of this project was to develop an understanding of main aspects of antibiotic use pattern in Norwegian hospitalised children and neonates; both during hospitalisation, and before and after hospitalisation. Thereby, we aimed to find focus areas for paediatric antibiotic stewardship and to increase the understanding of the connection between hospital and ambulatory antibiotic consumption.

The general aim was addressed through four specific aims:

1. To describe and compare antibiotic use in children in two different paediatric departments, a university hospital and a district hospital; with emphasize on total antibiotic use, adherence rate to the guidelines, distribution of antibiotic types with focus on BSA, indications, treatment-length, doses, comorbidities and blood cultures. [Paper 1]
2. To describe and compare antibiotic use in neonates in two different neonatal units, a university hospital and a district hospital; with emphasize on antibiotic exposure rates, proportion with confirmed infections, distribution of antibiotic types with focus on BSA, treatment-length, CRP values and doses. [Paper 2]
3. To investigate whether antibiotic use during hospitalisation was associated with increased use of antibiotics in ambulatory care before and after hospitalisation compared to the general paediatric population. Furthermore, to assess if the risk and pattern of antibiotic use in ambulatory care changed after hospitalisation compared to the period before hospitalisation. [Paper 3]
4. To investigate whether antibiotic use during the first three months of life was associated with increased use of antibiotics in ambulatory care during the following year compared to the general infant population. [Paper 4]

3. Materials and methods

3.1 General summary

This was an observational and explorative project based on children and neonates that received systemic antibiotics in two Norwegian hospitals during several months in 2017. Clinical data on antibiotic use in these hospitals were prospectively collected on a day-to-day basis. For paper 1 and paper 2, only these data were used. For paper 3 and 4, the clinical data from one of the hospitals were combined with national registry data on an individual patient level by using the NorPD [48]. Additionally, the Norwegian Population Registry was applied to establish a matched group of children and neonates that had not received antibiotics in-hospital during the same periods.

Throughout the thesis, the following age-range definitions are used: Neonates (children admitted to the neonatal unit), infants (children less than three months), children (up to 18 years except neonates or infants). In some contexts, I use children for all age groups, but this should be easy to recognize. Different terms and definitions used in the thesis and the papers are summarized in Appendix 1. In the following, I present an overview of the methods used in this project.

3.2 Hospital registrations

3.2.1 Design

These were periodical observational surveys of antibiotic use. The data were prospectively collected by project participants working at the wards. This design was chosen to follow antibiotic use pattern over time, and to have first-hand knowledge of the data collection to ensure high quality of the data.

3.2.2 Setting

The registration of antibiotic use was conducted in two different hospitals in Norway: Ålesund Hospital, hereafter called the district hospital (DH); and Ullevål University Hospital in Oslo, hereafter called the university hospital (UH). We chose these hospitals because they represent two different parts of the country and because of their distinction in academic attachment. Both departments treated children with infectious diseases from 0 to 18 years (up to the day of turning 18 years), and both hospitals also included highly specialised neonatal departments, treating neonates admitted from the maternity ward and critically ill children less than three months of age.

The demographic population numbers presented in the following paragraphs are based on public available data from Statistics Norway, the official source of basic demographic statistics in Norway [94]. The DH is located in the north-western part of Norway in the city of Ålesund, the 9th largest city in Norway with 64 720 inhabitants (2017). The hospital includes a wide range of medical and surgical specialties, and is the largest out of four hospitals in the county of Møre og Romsdal. The entire county consisted of 266 274 inhabitants in 2017, and the areal is 14 356 km^2. Most of the county is rural and consists of large mountain ranges and fjords, making fast road connections difficult; for several distances, transportation with ferries is necessary. Transportation with car to the DH could take up to four hours inside the catchment area. 57261

The paediatric department at the DH has regional services for the entire county and includes a general paediatric ward with 18 beds and a neonatal intensive care unit (NICU) with 13 beds. The NICU serves infants with gestational age (GA) ≥ 26 weeks; before February 2017, it also served those with GA < 26 weeks. The NICU provides all aspects of intensive care treatment such as invasive ventilation and hypothermia, except neonatal surgery and extracorporeal membrane oxygenation (ECMO). The NICU serves all four maternity wards in the county. The number of live births in the county in 2017 was 2681 (based on birth register data from the maternity wards). The paediatric ward includes both surgical and medical cases, including most paediatric conditions. Children in need of intensive care (such as invasive ventilation) are treated at the hospital`s general intensive care unit (shared with adults). Oncological patients are mainly treated at St. Olavs University Hospital in Trondheim, but some of the cytostatic treatments as well as events of neutropenic fever are delegated to the DH.

In 2017, there was one additional small paediatric department in the county located at Kristiansund Hospital in the northern part; this department provided eight beds (four during week-ends). It was also closed for about ten weeks throughout the year. When the department was full or in complicated cases, these children were often transferred to the DH in Ålesund. Taking this into account, our estimated number of children living in the catchment area of the DH in Ålesund in 2017 was 50 274. This was calculated by adding 40% (N = 4970) of the numbers of children living in the geographical catchment area of the hospital in Kristiansund (12 424), to account for the frequent use of the DH in Ålesund, also for these children. The remaining 60% (7454) of these were excluded to account for the capacity of the hospital in Kristiansund. Even though this estimation is not 100% accurate, we regard it adequate for our purpose.

The UH is located in Oslo, the capital of Norway, with 666 759 inhabitants (2017). It is situated in the south-eastern part of the country, and the distance from the DH is 376.3 km (straight line). The paediatric department is divided in several wards, including an infectious disease and observational ward (18 beds), and a NICU (27

beds). The hospital also serves a separated paediatric surgical ward, a paediatric intensive care unit and a general paediatric ward. The NICU provides treatment for neonates for all GA groups, and all aspects of intensive care except ECMO and thoracic surgery. The number of live births at the UH in 2017 was 7014 (data from the maternity ward). Also, critically ill or extremely premature neonates born at nearby local hospitals could be transferred to the UH. Children with infectious diseases in Oslo are mainly treated at the infectious disease and observational ward at the UH. The exceptions are children with oncological conditions, immunodeficiencies or severe cardiologic conditions; these children are most commonly referred to the other paediatric department in Oslo at Rikshospitalet university hospital. The UH is a referral centre for children with cystic fibrosis (CF) for the entire country. The number of children in the uptake area of the UH (defined as the number of children living in Oslo) was 137 233 in 2017. Transportation time to the UH is short (within one hour) for all patient living in the catchment area.

3.2.3 Participants and time-periods

At the DH, we recruited all children 0-18 years that received systemic antibiotics during their admission from 1st of January to 31st of December, in 2017. At the UH, we recruited all children 0-18 years that received systemic antibiotics at the infectious disease and observational ward from 1st of June to 31st of July and from 17th of October to 17th of December, in 2017. From 1st to 31st of July we also recruited patients from the general paediatric ward, because the wards were merged together for this period (summer holiday). At the NICU, patients were recruited from 27th of March to 20th of May and from 1st of October to 31st of December.

3.2.4 Data collection and variables

Data collection was conducted every day at 8 AM using a registration scheme (Appendix 2) based on variables recommended in the point-prevalence protocol of the European Centre for Disease Prevention and Control [95]. At the DH, nurses working at the ward performed the data collection supervised by the project manager. At the UH, three different paediatricians did all the registrations. Educational classes were held

before the start of the data collection. Data was collected by using the medical chart, by questioning the ward-physician responsible for the patient, and by using the electronic patient record. The project manager performed a secondary control of all variables before they were plotted into an electronic database securely stored and without directly identifiable variables.

The following variables were collected in both children and neonates: Total number of patients admitted to the wards, total number of patients receiving antibiotics, national identification numbers, county of residence, gender, age and weight at the start of the antibiotic course, type and dose (including intervals) of antibiotics, route of administration, indication for antibiotic use and whether it was for treatment or prophylaxis. Furthermore, in children we registered comorbidities, whether the infection was healthcare or community acquired, results from sterile bacterial cultures and results of airway cultures from patients with CF. In neonates we registered GA at birth, birthweight, weight at the start of the antibiotic course, delivery mode, maximum CRP value (mg/L), if respiratory support was given, neonatal complications/other conditions and results from blood cultures. For children less than three months admitted to the general paediatric ward at the DH, GA at birth was also collected retrospectively through the electronic patient record. For children and neonates receiving antibiotics at the beginning and at the end of the registration period, we collected information on how many days before/after they received antibiotics for the same indication, only to be used for calculating treatment length. Total numbers of live births in the uptake areas during the collection periods were collected from the respective maternity wards. According to the Anatomical Therapeutic Chemical (ATC) classification system, we defined antibiotics as systemic antibacterials (J01), oral vancomycin (A07AA09) and oral metronidazole (P01AB01) [49].

The registration of comorbidities (children) and complications/other conditions (neonates) was based on predefined lists (see Appendix 3). For children, the selection of comorbidities could be challenging. One opportunity could have been only to include those with certain conditions directly increasing the infection risk such as

immunodeficiencies and CF. However, our mission was to include most moderate to severe underlying somatic medical conditions to reflect the broad picture of children receiving antibiotics in-hospital. Common mild conditions such as enuresis, acid related disorders in infancy and asthma without daily medication were not included. We used the categories in Paediatric Complex Chronic Conditions Classification System version 2 as baseline for our assessment [96]. If more than one comorbidity was present, we only registered what we regarded the most severe condition. In neonates, registration of comorbidities is challenging, as they may not have developed at time of admission to the NICU. Thus, we aimed to register typical severe neonatal complications, such as treatments with hypothermia and invasive ventilation, and severe conditions that had occurred already in the first period of life. The aim was to sort out a group of neonates with particular increased vulnerability for the follow-up study.

The indication for antibiotic use was based on the treating physicians note in the electronic medical record and/or oral statements to the data collectors. An alternative would be to register indications based on inclusion criteria for specific diagnosis. However, as we wanted to access antibiotic use in relation to suspected diagnosis by the treating physician, we regarded this the best way of noting this information. We merged indications together in the following main categories: pneumonia, upper respiratory tract infections, urinary tract infections, infections in bone, joint, skin and soft tissue, central nervous system (CNS) infections, intra-abdominal infections, sepsis, surgical prophylaxis, medical prophylaxis. For further descriptions of the other variables that we collected, see paper 1 (children) and paper 2 (neonates).

3.3   Follow-up through the Norwegian Prescription Database

3.3.1 Design

The follow-up studies were designed as explorative matched data-linkage cohort studies, using the patients from the hospital registration at the DH as a cohort having the common characteristic of being prescribed antibiotics in-hospital during 2017. Through the NorPD we could assess all ambulatory prescriptions of these patients before and after hospitalisation. Through the Norwegian Population Registry we could establish a matched reference group for comparison.

3.3.2 The Norwegian Prescription Database

The NorPD is a national prescription database administered by the Norwegian Institute of Public Health, and has existed since 2004 [48]. It is regulated by the national Health Register Act [97]. The database contains information on all prescriptions dispensed to individual patients in ambulatory care. Information include type of medicine, formulation, size of package, whether the prescription is reimbursable and the date of dispensing. The national identity number is encrypted, but can be reverted and by that make it possible to link to other registries or – in our case, a study database with national identity numbers. In Norway, antibiotics for humans are only available through prescriptions from selected health care workers such as medical doctors and dentists. Therefore, all ambulatory antibiotic courses dispensed in Norway could be traced through the NorPD. The capture rate is regarded to be close to 100%. Hospitals and other healthcare institutions buy a storage with antibiotics directly from the hospital pharmacy. Thus, individual inpatient antibiotic use cannot be tracked through the NorPD.

3.3.3 Participants and time-period

All children recruited during the hospital registrations at the DH in 2017 were eligible for the follow-up studies. The follow-up studies were divided in one for children of three months or more (paper 3) and one for infants less than three months (paper 4),

regardless if they were recruited from the NICU or the general paediatric ward. This was regarded a reasonable cut-of given that three months of age marks the end of the prolonged neonatal period; clinicians are trained to be particular careful with children less than three months presenting with infectious symptoms such as fever.

Exclusion criteria was loss of follow up due to death, if any children/parents chose to withdraw from the study, or if registered residency was not in Møre og Romsdal. We preferred to have a study population and matches from the same county to avoid eventually geographical confounders during follow-up, for instance different geographical prescribing culture or local outbreaks of infectious diseases. All included children and infants were followed individually with regard to antibiotic prescriptions during one year before the month of hospitalisation (or from birth in children less than 12 months) and during one year after the month of hospitalisation, excluding the month of hospitalisation.

3.3.4 Matched group from the general population
Included children from the general population were identified from the National Populating Registry and randomly selected based on matching criteria [98]. The register contains information on all persons that resides or have resided in Norway. Each child and infant from the hospital registration was matched with ten children from the general population according to sex, month and year of birth, and county of residence. These ten children were followed for the exact same period as the child who had received antibiotics in-hospital.

3.3.5 Data collection and variables
Children from the hospital registration were connected to their NorPD prescription history according to ethical procedures guided by the NorPD. Likewise, the matched children from the Norwegian Population Registry were connected to their NorPD prescription history. The final database included all antibiotic prescriptions registered from 1th of January 2016 to 31th of December 2018. We included information on formulation, size of package, whether the prescription was reimbursable and date of

dispensing. In Norway, antibiotics can be prescribed as an reimbursable prescription if certain criteria related to increased infection risk are fulfilled such as if the doctor suspect that the patient will need antibiotics for at least three out of 12 months; or in chronical conditions such as recurrent urinary tract infections, immunodeficiencies, certain chronical lung conditions and cancer [48].

3.3.6 Comorbidity assessment

Two different methods were used to assess comorbidity through the NorPD. For the reference group from the general population, we collected information on other medical prescriptions than antibiotics. These were used as proxy for comorbidity in paper 3 (see Appendix 1 for detailed descriptions). Furthermore, we used reimbursable antibiotic prescriptions as proxy for comorbidity in both paper 3 and 4.

We could have included information on other medical prescriptions than antibiotics also for the hospital population, but we decided to use the comorbidities registered during hospitalisation (children, paper 3), as this was regarded most accurate. Obviously, the different methods could create problems as they are not directly comparable. Not all moderate/severe comorbidities are treated with medications, and these would not be detected through the NorPD. Therefore, we also assessed antibiotics prescribed as reimbursable prescriptions in both groups, both for infants and children. We were aware of the limitation of using reimbursable prescriptions; it would only select children with clearly increased infection risk and not all with moderate/severe comorbidities. The advantage would be the direct relevance to increased risk of antibiotic use. For infants in particular this was an opportunity to detect those developing infection-related comorbidities during the follow-up period.

3.3.7 Power calculations

Before the follow-up studies, we performed power calculations in order to include a reasonable number of children and infants. Based on public statistics from the NorPD [48], we assumed that 15% in the reference groups (both children and infants) would receive at least one prescription of antibiotics the following year after discharge. As

this was an explorative study, it was difficult to assume what the proportion would be in the hospitalised children and infants. Based on the impact of comorbidity, we considered 25-30% (10-15% difference) to be an appropriate estimation for power calculations, also with regard to clinical relevancy. To detect such a difference with a statistical power of 85% and with ten times as many children/infants from the reference group, we would need at least 69-148 in each group of children/infants compared to 690-1480 children/infants in the reference groups. For total number of prescriptions, assuming 0.20 prescriptions per child/infant in the reference groups [48], and 0.26 prescriptions per child/infant in the hospital groups, we would need at least 27 children/infants from the hospital registrations in each group and 270 in each reference population. This was based on the same reasoning as explained above.

Based on admission statistics from the paediatric and neonatal ward in the DH from 2016 (Appendix 4) and available literature from Norway on proportion of inpatients treated with antibiotics [54, 81], we regarded that one-year registration period at the DH would ensure a high enough number of patients for our purposes. However, we realised that the number of infants only recruited from the NICU could be in the lower range of the desired area; expecting that 25% of 310 admitted infants in 2016 received antibiotics, this would lead to 78 recruited infants. However, as we also aimed to include infants less than three months from the paediatric ward, we expected this number to rise.

3.4 Analyses and statistics

3.4.1 Antibiotic use in children during hospitalisation (Paper 1)

In this paper we aimed to describe and compare antibiotic use pattern in children between the DH and the UH. The three main outcomes were the proportion of treatments involving BSA, the proportions of treatments given in adherence with the Guideline and the prescribed dose for the most commonly used antibiotics. Other important outcomes were proportion of patients on antibiotics, proportion of children

with comorbidities, distribution of treatment indications, obtainment rate of blood cultures including description of pathogens, distribution of all antibiotic prescriptions, and specifically the distribution of BSA prescriptions and their relation to comorbidities and guideline adherence.

In this paper, each admission counted as one patient. We regarded this the most relevant measure as we aimed to study the total impact of all admissions and include one admission as one unique story. We excluded children treated for surgical conditions, and children receiving antibiotics as prophylaxis. In order to get an impression of the quantity of consumed antibiotics, there are several options for describing this [18]; we assessed the antibiotic exposure rate, but also the total number of prescriptions related to bed-days (total number of occupied beds). Finally, as some children may received more than one antibiotic treatment due to different indications during the same admission, we also assessed number of treatments/courses. For doses, we reported mg/kg/day for children less than 40 kg. See Appendix 1 for further details.

When calculating adherence rate to the Guideline, we based this on the first-line antibiotic recommendations [87]. We also chose to include treatments in accordance with susceptibility findings from our defined bacterial isolates as appropriate equal to "in adherence with the Guideline". All tested susceptible antibiotics were accepted. Even though an antibiotic treatment is acceptable according to susceptibility findings, it is not necessary the best option in terms of ecology or clinical evidence. However, we found it challenging to select appropriate antibiotics within those that were susceptible; these few cases would often be severe and various acceptable reasons (that we could not target) regarding antibiotic choice could justify the decision. We also found it useful to include respiratory tract isolates in patients with CF; in these children, one generally emphasizes the use of BSA based on the high frequency of challenging infections with bacteria such as *Pseudomonas Aeruginosa*.

In the comparative analyses between the UH and the DH we used chi-square test for proportions. For small samples, the chi-square test is an approximation and Fischer's

exact test is considered to be better. We used chi-square test throughout. For those comparisons where sample size were small (any expected frequency less than 5), we also did the analyses using Fischer's exact test and since conclusions or p-value significant levels did not change, the chi-square test was considered to be a good approximation. Student`s independent sample`s t-test (two-tailed) was used for means and Moods median test for medians. We used Fisher`s exact test to compare the distribution of indications in relation to specific antibiotics as a control measure when comparing doses. We used multivariate logistic regression to adjust for age as an independent variable in the comparison of BSA use and the adherence rate to the Guideline. For means, the standard deviation (SD) was calculated and for medians, interquartile range (IQR) was calculated. Some variables were not regarded comparable between the hospitals because of case-mix. For more details on definitions, analyses and statistics, see paper 1.

Additionally, in this thesis I present some few additional results. I report admissions and prescriptions per 1000 children in the uptake area per year. This was calculated based on numbers provided in the paper. For this purpose, the number of admissions and prescriptions for the UH were multiplied by three to cover one year.

3.4.2 Antibiotic use in neonates during hospitalisation (Paper 2)

In this paper, we aimed to describe and compare antibiotic use pattern in neonates at the DH and the UH. The main outcomes were antibiotic exposure rates the first three days of life in relation to number of live births, the proportion of neonates treated for suspected sepsis that had a confirmed or unconfirmed infection and treatment length in unconfirmed sepsis. Other important outcomes were distribution of antibiotic prescriptions including BSA, mean maximum CRP value in relation to treatment days, and dosing of the most commonly used antibiotics in term infants.

The inclusion and definitions of variables to describe antibiotic use were the same as for children, see Appendix 1. A confirmed infection, in addition to blood culture positive cases, was defined according to the definition of culture-negative neonatal

sepsis by the Norwegian Neonatal Network [99]; suspicious symptoms, a maximum CRP value of 30 or more and treatment of at least five days (or death before five days).

Findings were mostly described separately according to different gestational age: Term infants (GA ≥ 37 weeks), premature infants (28-36 weeks) and extremely premature infants (< 28 weeks). In extremely premature infants, only merged results from both hospitals were presented, except basic demographics. In some cases, it could be difficult to determine whether one should classify cases as treatment or prophylaxis because symptoms of sepsis could be subtle and mimic other common neonatal conditions. We decided to classify all cases where a blood culture was obtained as treatment. We regarded that the obtainment of blood culture reflected that an active infection was an opportunity.

We used the chi-square test to compare selected proportions, but as for children we also used Fisher`s exact test for low numbers to control that chi-square was an appropriate approximation. We used Student`s independent sample`s t-test (two-tailed) for means and Moods median test for medians. Both means and medians were presented with corresponding 95% CI`s. For the relationship between CRP values and treatment length, we estimated Pearson's correlations coefficient. For more details on definitions, analyses and statistics, see paper 2.

3.4.3 Ambulatory antibiotic use in children (Paper 3)

In this paper, we aimed to explore ambulatory antibiotic use in our cohort of children who had received antibiotics in-hospital (H+). We studied the use one year before and one year after hospitalisation to examine the risk of use compared to a reference group that had not received antibiotics in-hospital (H-). We also studied whether the risk changed before and after hospitalisation. The primary outcome was the relative risk (RR) of antibiotic exposure in ambulatory care before and after hospitalisation for children in the H+ group compared to the H- group. The secondary outcome was the incidence rate ratio (IRR) of total number of prescriptions in ambulatory care before

and after hospitalisation for children in the H+ group compared to the H- group. Another important outcome was the RR of exposure for different types of antibiotics.

Primary and secondary outcomes were presented with and without comorbidity-adjustment, and separately for girls/boys and three different age groups. Our primary outcomes were also presented for additional subgroups defined by treatment characteristics in-hospital for the H+ group. These subgroups included indication for antibiotic treatment in-hospital, duration of treatment, if the child was admitted to hospital more than once, and if the child had been exposed to BSA in-hospital. When selecting these subgroups, we emphasized the clinical additional value these variables might had when doing the all-over interpretation of the findings, and that a reasonable number of children could be selected to these subgroups. For definitions of comorbidities and terms used in relation to antibiotic use in paper 3, see Appendix 3 and 1, respectively.

We used the log-binomial regression model and the log-link function to calculate RR and the negative binomial regression model to calculate the IRR, both with corresponding 95% CI. Furthermore, due to matching, we estimated robust standard errors in both models. Differences in RR and IRR before and after hospitalisation were tested by including a period-by-group interaction term in the analyses. To account for repeated measure and intra-individual correlation, we used generalized estimating equation methodology assuming an exchangeable correlation structure. In addition to the results presented in the paper, I do in the thesis also present an overview of the distribution of all antibiotic prescriptions. For more details of analyses and statistics, see the methods section in paper 3.

3.4.4 Ambulatory antibiotic use in neonates (Paper 4)

The aim of this study was to examine one-year subsequent antibiotic use pattern in infants who had been exposed to antibiotics during hospitalisation in the first three months of life (AB+), and to target whether these infants had increased risk of recurrent antibiotic use compared to a general population of infants, matched

according to age, residency and gender (AB-). The main outcome was the RR of antibiotic exposure during one year after the first event of exposure in the AB+ group relative to the AB- group. The secondary outcome was the IRR of the total number of prescriptions in the AB+ group compared to the AB- group. Furthermore, we also presented a proportional distribution of the most commonly antibiotics used in ambulatory care in both groups.

The analyses were performed with and without comorbidity adjustment, and we performed separate analyses for boys and girls and for those who received certain oral broad-spectrum antibiotics in ambulatory care: Macrolides, co-trimoxazole, clindamycin, cephalexin and ciprofloxacin. Furthermore, we did several subgroup analyses based on AB+ specific characteristics; GA (divided in term infants and preterm infants), infants needing respiratory support and infants treated with antibiotics in-hospital for at least five days. We also did separate analyses for low-risk term infants, defined as term infants without neonatal complications/other conditions, assuming these would have less risk of subsequent ambulatory antibiotic use.

For definitions of comorbidity and terms used in relation to antibiotic use, see appendix 1 and 2, respectively. Also, note that in paper 4, antimicrobial is used throughout instead of antibiotic, while in this thesis and in all the other papers, antibiotic is used. However, the definitions were identical.

We used the log-binomial regression model including the log-link function to estimate RR of recurrent antibiotic exposure in the AB+ group compared to the AB- group, and the negative binomial regression model to estimate the IRR of total antibiotic prescriptions in the AB+ group compared to the AB- group. Due to the matching, we estimated robust standard errors to account for possible correlation. We presented a proportional overview (using percentages) of the different antibiotics used, but only one prescription per antibiotic was included. We were aware that the power calculations were performed for the all-over analyses and that subgroup analyses that were decided afterwards would have less statistical power. Despite this, we believed

that subgrouping would help in understanding the all-over results. We regarded that the 95% CI would give a precise presentation of the credibility of the results. Also, post-hoc power calculations are not recommended [100]. For more details of analyses and statistics, see the methods section in paper 4.

3.5 Ethics

The entire study and its methods was approved by the Regional Committee for Medical and Health Research Ethics (2017/30/REK Midt). The data collection at the hospitals in Ålesund and Oslo were also approved by the Local Data Protection Officer at the two hospitals, and at Haukeland University Hospital in Bergen, as most of the data analyses were performed on their data-server. Information letters with the option to withdraw from the study were sent to all participants according to the recommendation from the ethical committee.

A list with the national identity numbers of the participant from the hospital registrations is kept in a locked drawer, and only one of the project-members has the key. A connection number has been used when working with the data electronically. The de-identified datasets are stored on a secure server approved for research according to the rules of Haukeland University Hospital.

The National Population Registry handed over data directly to the NorPD, and the further transfer of data from NorPD was performed according to their ethical procedures.

4. Methodological considerations

When conducting observational research, it is important to consider the different possibilities of study designs and the internal and external validity of the data used. Our study concept was observational and explorative.

4.1 Study design

4.1.1 Hospital collection of antibiotic use

When aiming to describe antibiotic use in hospitals there are different designs that could be considered. One option is a retrospective design collecting data from the electronic journal system; the advantage of this would be less use of resources for day-to-day data collection, and more easily include a larger group of patients. However, the identification of children that had received antibiotics would be challenging and unpredictable as identification has to be based on diagnostic codes in the hospital administration search system. Moreover, collecting information from journal notes and scanned medical charts, could lead led to lack of or misinterpreted information (information bias) as these notes are not written in scientific purpose. Electronic medical charts were not available in paediatric departments in Norway at the time of our data collection (2017) and could therefore not be considered as an option of surveying antibiotic use, but may represent a great possibility for the future.

In neonates, we considered using data from a national neonatal registry that contain data from all neonatal admissions in Norway [93]. However, important parameters that we aimed to examine such as antibiotic doses and CRP values are not collected for this registry; also, the collection is performed by many collectors, increasing the risk of information bias. Additionally, we found it most feasible to use the same prospective day-to-day clinical collection in both the paediatric departments and at the NICUs. Furthermore, as a previous study had presented antibiotic use data from this registry [81],

we found it appropriate to contribute to the topic using another data collection method, strengthening the total interpretation of neonatal antibiotic use in Norway.

A commonly applied option when monitoring antibiotic use is using PPSs. These are usually one-day surveys of antibiotic use. Conducting a PPS is not very time consuming or resource demanding which is an advantage. This also makes it easier to include more hospitals to merge and compare data from different settings. However, using data from one single day (or a very short period) could be problematic, especially in a small country like Norway. These surveys only capture a very little number of children with individual conditions. In addition, paediatric wards generally consist of less patients than adult wards and particular caution must be taken not to misinterpret the information. Furthermore, short collection periods are more vulnerable to casualties like epidemics limited to certain geographical areas. Another method of measuring antibiotic use that we considered was using sale statistics from the hospital pharmacy, this method is used in the NORM reports [18]. However, using such data in children would only be useful for a very basic overview and eventually to follow year-by-year trends in one single centre; the amount of antibiotics sold to the wards is neither consistent with the amount of antibiotic actually used in the wards [101]. The lack of individual patient data is problematic in children who have a much greater variation in doses than adults.

Our research group previously published antibiotic surveillance data from Norway based on eight PPSs conducted quarter wise. The use of repetitive surveys limited some of the problems explained above. However, using registry data for such a purpose could also be problematic as external collectors manually collected these data. Moreover, important information such as body-weight, treatment length and comorbidity was missing. By having first hand responsibility and knowledge on the data collection, we decided to use prospectively registrations performed by project members during a longer period in this project. We also regarded that it would be useful to supplement our point-prevalence data using another method.

4.1.2 Follow-up through the NorPD

When we planned this study, we questioned whether it would be more appropriate to describe ambulatory consumption pattern in children from the hospital registrations without any reference group. Since the reference group from the general population was expected to be healthier, one could argue that the two groups were not directly comparable. To cope with this, the groups were matched in accordance with age (in months), county (Møre og Romsdal) and sex, which else could have been important confounders. Furthermore, we collected information on comorbidities in both groups (Appendix 3). Besides this, the remaining uncertainty associated with such an explorative comparison was regarded acceptable given that one carefully discusses reasons for different antibiotic use without too strong conclusions. We regarded that it was interesting enough itself to estimate approximately how much and what antibiotics such a population as ours would use. In addition, we found it useful to have a reference group to better picture out the difference in antibiotic use; without a matched reference group, one would automatically compare the findings against unmatched public available data from the NorPD. Also, to compare antibiotic use rate before and after receiving antibiotics in-hospital, we regarded that it was crucial to have a reference population; this would decrease the influence of specific events such as unusual outbreaks of microorganisms, change in guidelines/practice and also age dependent variation in antibiotic use. We considered including a reference group also from the hospitalised paediatric population to better understand the impact of being hospitalised itself, but concluded that this was not feasible or necessary.

Finally, we realize that sample size was low for some of the subgroup analyses, but for the main statistical analyses, we regarded the sample size adequate according to our power calculations made in advance.

4.2 Internal validity

The most common systematic errors in an observational study are bias and confounding.

4.2.1 Bias

Selection bias is a systematic error due to the methods used to recruit study participants and from factors influencing study participation [102]. This is the type of bias that most of all influenced our studies. The advantage of choosing the selected hospitals was their distinction regarding localization, size and academic attachment. The challenge was the comparability and case-mix of patients; these paediatric centres had different ward-structure, geographical infrastructure and some differences in patient population characteristics leading to a degree of selection bias, most of all for children after the neonatal period. To cope with the lack of recruitment from several paediatric wards at the UH, certain groups of patients from the DH were excluded for paper 1; surgical paediatric patients and children receiving antibiotics as prophylaxis. We regarded that major differences in clinically important measures such as BSA use, adherence to guidelines, doses, indications for antibiotic treatments and number of confirmed infections (neonates) could be detected. Furthermore, we regarded that data descriptions from both hospitals separately would be interesting enough itself; we aimed to explore antibiotic use and potential differences, and to discuss potential reasons.

Optimally, we would register antibiotic use for one entire year at the UH and to include all the paediatric wards, but this was not possible due to limited resources. We regarded that the distinction in collection periods could lead to selection bias in children due to seasonal variation by influencing the frequency and distribution of indications for antibiotic treatment. We could have limited the presentation of antibiotic use at the DH to the same periods as in the UH, but this would have limited the power of the DH population drastically. Thus, we decided to keep the different registration periods, but to make separate analyses including matched time-periods to

control for the seasonal variation (paper 1). Ultimately, based on the total number of children living in the respective uptake areas (almost three times higher at the UH), we regarded a four month collection period from the UH to give a total number of study participants in the same range as in the DH.

Close relationship to the participating wards, as in our study, could potentially affect antibiotic use decision, creating a registration bias. However, this would be equal for both hospitals, but should be taken into account when comparing results with other studies and settings. However, there was no specific antibiotic stewardship programs at the hospitals during the study periods, and we assume that prescription patterns are difficult to change by a great manner without new guidelines or specific stewardship efforts. We also regarded the advantage of a close knowledge of the wards as important so that we were able to closely follow up the registration, and ensure high quality of the collected data.

In the follow-up studies, we intended to include all children and neonates receiving antibiotics in-hospital in our county during 2017. However, as there is one more small paediatric department in the county (but without a neonatal unit) we cannot exclude that there may have been some children in the reference group (that was matched according to county of residence) that were given antibiotics in this hospital. We can neither exclude that any of the patients in the reference group were given antibiotics in-hospital during traveling to other counties or abroad. This could create a selection bias, but we regarded that this only would be relevant for a very few number of children.

Information bias is a systematic error due to incorrect measurement or classification of the exposure or outcome variable being studied [102]. We regarded the risk of information bias small as all variables during the hospital collection were based on information recorded in the patient record and from the treating physician. Despite this, minor differences between collectors in the interpretation of for instance comorbidity criteria could have occurred. However, data were double-checked by the

project leader to minimize the risk of information bias. Data from the NorPD derive from a high-quality national register organized by the Norwegian Institute of Public Health and have a capture rate close to 100%.

4.2.2 Confounders

Confounding is when a third factor is the reason for all or part of the observed association between the exposure and the outcome being studied [102].

In the description and comparison of antibiotic use between the hospitals, we adjusted for age as a possible cofounder for the main analyses in paper 1, and we controlled for indication as a possible confounder when comparing doses between the hospitals. We did not adjust for comorbidities, but we described comorbidity rates separately and for all indications in order to study its impact. In paper 2, data from extremely premature neonates were described separately and merged together from both hospitals.

The follow-up studies were subject to confounding by indication as other causes than antibiotic use during hospital admission possibly could explain the risk for antibiotic use in ambulatory care. We regarded medical comorbidities as the most obvious confounder. Others could be hospitalisation itself and various factors related to behaviour, cultural and psychological factors in parents and/or prescribers. If concluding the role of antibiotic administration in-hospital per se was crucial, a randomized control trial would have been the best option to target this. However, it would be problematic from an ethical point of view to randomly select hospitalised children to antibiotic therapy or not. This strategy would be better suited for examining the efficacy of antibiotics for certain clinical conditions where their role remain unclear. Our study was observational and explorative and did not aim to conclude the exact reason for increased or decreased ambulatory antibiotic use; we wanted to include the whole surrounding of receiving antibiotics in-hospital. However, as explained in the methods section, we performed several adjustment analyses for comorbidities to capture the impact it had on ambulatory antibiotic use as accurate as possible. In addition to comorbidity adjustments, we included subgroup analyses of

specific variables related to hospital admission, for instance treatment indications, length of treatment, complications and prematurity, to access risk for these children separately. Other possible confounders such as age and residency were matched variables between the groups. Despite this, ruling out all confounding that different degrees of medical comorbidities might cause is difficult.

4.3 External validity

External validity, generalizability, is the ability to generalize results and conclusions from the population being studied to other populations [102].

Antimicrobial resistance and antibiotic use pattern vary between countries [9, 20, 46, 55, 56]. Furthermore, we only included children from a small part of Norway that could also limit the national generalizability. Antibiotic practice in ambulatory care vary between different parts of Norway, but this is also why such field studies of antibiotic use that we have conducted is of high importance. Even though this is a limitation in the generalizability of the practice itself, descriptions and comparisons of antibiotic use pattern in different settings are important and interesting for all involved in paediatric antibiotic prescribing to get a holistic picture of practice. In addition, antibiotic guidelines in Norway are national, and there is a strong collaboration in the paediatric society and between hospitals. We regard that learning points and aspects in antibiotic use is generalizable to other hospitals, also outside Norway, especially in paediatric departments with a comparable background population. Eventually important differences in practice between a district hospital and a university hospital could also possible be generalized. Also, relevant for the follow-up studies, publicly available data from the NorPD show that ambulatory antibiotic use rates in Møre og Romsdal in 2017 were very similar to the national rates [48]. This increases the external validity of our results in the follow-up studies.

5. Results and discussion

5.1 General

To our knowledge, this is the first study describing in-hospital antibiotic use in children including inter-hospital comparisons, and at the same time monitoring ambulatory antibiotic use in the same patients. The originality of the study lies both in the selection of two different hospitals, and in the connection of antibiotic consumption data between prospectively collected clinical data from hospitals and the national prescription registry for ambulatory care. The different papers each contributed to the aim of detecting areas of importance for paediatric antibiotic stewardship.

Overview of study participants

None of the eligible study participants chose to withdraw from the study. Thus, all children and neonates receiving systemic antibiotic on the included wards were recruited to the studies that used data from the hospital registrations only (paper 1 and 2). For the follow-up studies through the NorPD at the DH (paper 3 and 4), eight participants were excluded; one died during the period, and seven did not have their home address in the county of Møre og Romsdal. Figure 4 shows a basic overview of the study design including the timeline and number of participants in all four papers. Figure 5 shows more details of the participants recruited from the DH.
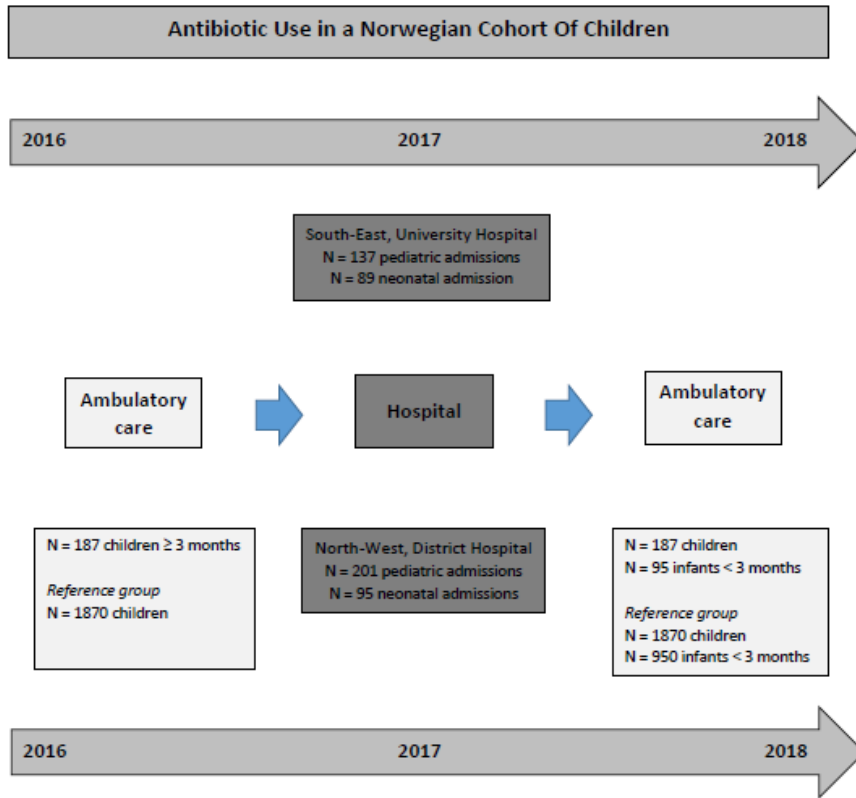
Figure 4. Flowchart representing all four papers in the thesis including the number of children recruited to the studies. The baseline for all papers are the children recruited during hospitalisation in 2017. The piles indicate the correlations between different selections of children and their relation to the timeline.

[1] For ambulatory care, all children receiving systemic antibiotics in-hospitals were included, while in the hospital registrations surgical admissions and admissions related to prophylactic use of antibiotics were excluded.

Paper 1
201 pediatric admissions

42 admissions excluded
(surgical patients and
prophylactic use)

Paper 2
95 neonatal admissions

None excluded

Baseline data
338 admissions represented by
290 unique children/neonates

243 admissions to pediatric ward
95 admissions to neonatal ward

Paper 3
235 admissions representing 187
unique children ≥ 3 months

2 admissions/children excluded

Paper 4
95 admissions representing
95 unique infants < 3 months

6 admissions/infants excluded

Figure 5. Number of admissions and children recruited at a Norwegian district hospital, and how these numbers were used in the different papers.

5.2 Summary of main results and implications

In the following, we present two figures connecting the findings from all papers together. Figure 6 shows selected main results in relation to all parts of the thesis, while Figure 7 summarises suggested focus areas for antibiotic stewardship in our population that we think could be useful for the entire paediatric environment when planning strategies to optimize the use of antibiotics in the future.

2016 | **2017** | **2018**

Children ≥ 3 months
- 44% were exposed to antibiotics
- 1.5 prescriptions per child

Compared to reference group
- RR of exposure: 2.9 (95% CI 2.4-3.5)
- IRR of total prescriptions: 6.8 (5.0-9.3)

Children
- Comorbidity: 1/3 of all children
- Adherence rate to the guideline: 3/4 of all treatments, 1/2 of pneumonia treatments
- Use of BSA: 21% of all treatments
- Of all BSA prescriptions: 2/3 given to children with comorbidities
- More treatments for pneumonia at the DH
- Variation in dosing within and between the hospitals

Children ≥ 3 months
- 46% were exposed to antibiotics
- 1.8 prescriptions per child

Compared to reference group
- RR of exposure: 2.8 (95% CI 2.3-3.3)
- IRR of prescriptions: 6.1 (4.4-8.3)

Ambulatory care → **Hospital** → **Ambulatory care**

Neonates
- 4/5 neonates (GA ≥ 28 weeks) treated for suspected EOS did not have confirmed infection and were treated for 3.1 days (mean)
- 2/3 neonates (GA < 28 weeks) treated for suspected sepsis did not have confirmed infection and were treated for 4.3 days (mean).
- Variation in dosing and choice of aminoglycosides between the hospitals

Infants < 3 months
- 23% were re-exposed to antibiotics
- 674 prescriptions per 1000 infants
- Penicillin: 48% of prescriptions

Compared to reference group
- RR of exposure: 1.7 (95% CI 1.1-2.5)
- IRR of prescriptions: 2.8 (1.6-4.9)
- Low-risk term infants, comorbidity-adjusted RR of exposure: 2.1 (1.3-3.7)

Figure 6. Summary of selected main results from all parts of the thesis including antibiotic use in children and neonates before, during and after hospitalisation in the period 2016-2018.

[1] RR; relative risk, IRR; incidence rate ratio, BSA; broad-spectrum antibiotics (cephalosporins except first generation, carbapenems, quinolones, piperacillin-tazobactam), EOS; early-onset sepsis, GA, gestational age, DH; district hospital
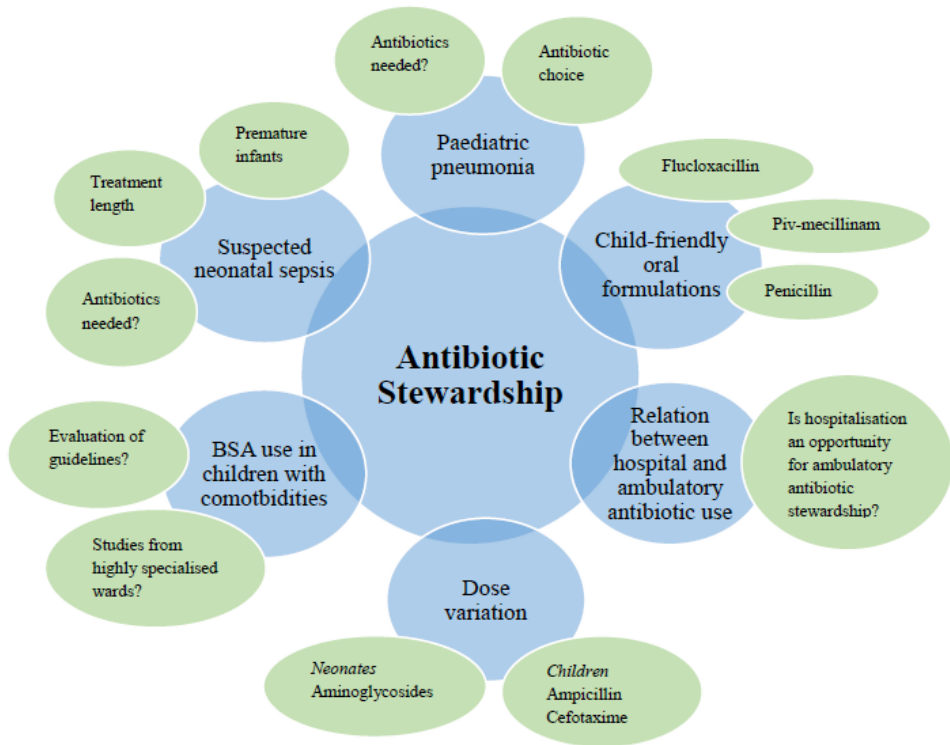
Figure 7. Selected focus areas for antibiotic stewardship strategies in children that we purpose based on this thesis

[1] BSA; broad-spectrum antibiotics (cephalosporins except first generation, carbapenems, quinolones, piperacillin-tazobactam)

5.3 Improving antibiotic use in hospitalised children (Paper I)

Two hundred and one paediatric admissions including antibiotic treatments and 638 antibiotic prescriptions were reported at the DH, referring to 4 admissions and 13 prescriptions per 1000 children in the uptake area per year. At the UH, 137 paediatric admissions including antibiotic treatments and 744 antibiotic prescriptions were reported, referring to 3 admissions and 16 prescriptions per 1000 children in the uptake area per year. The proportion of bed-days with any antibiotic was 27% at the DH and 29% at the UH. In general, antibiotic use rates in our population was in the same range as in a previous national PPS [54], but low compared to most surveys from other countries worldwide [51, 55, 103-107].

Aminoglycosides, aminopenicillins, betalactamase-sensitive penicillins and betalactamase-stable penicillins accounted for 60% of all antibiotic prescriptions at the DH and 55% at the UH. In a report from a Norwegian paediatric department in 2002, the corresponding proportion of the same antibiotics was 67% [67]. This indicate that these antibiotics have been the cornerstone in paediatric in-hospital treatment in Norway for several decades. Corresponding rates based on surveys from a selection of other European countries are 13-22% [55, 56].

In the following, I present three selected areas that we identified as important for future antibiotic stewardship strategies in hospitalised children.

5.3.1 Use of BSA

Reduction in the use of BSA is one of the main aims in the Norwegian Strategy against Antibiotic Resistance [21]. Of all antibiotic treatments in our study, 19% involved a BSA at the DH, while 24% involved a BSA at the UH. In total, 90% of all BSA prescriptions were given to children with comorbidities (68%), CNS infections (16%) or in accordance with microbiological susceptibility pattern (48%). CF was the dominating comorbidity in both hospitals.

To compare, in the previous Norwegian PPS, 32% of children on antibiotics prescribed by a paediatrician were given BSA [54]. Importantly, the national survey also included highly specialized wards such as large oncological wards. Compared to most international surveys, the children in our study received clearly less BSA [52, 55, 56, 103, 104], but in a Dutch paediatric department, very comparable to the DH, the proportion of BSA prescriptions seemed only slightly higher than at the DH [107].

Knudsen et al. published an interesting study revealing higher levels of enterobacteria resistant to ampicillin and co-trimoxazole in children with CF compared to a control group, but resistance to third-generation cephalosporins and gentamicin was low in both groups [108].

All-over, we did not find reasons to believe that practice of BSA use was different at the DH and the UH. We could neither conclude great potential for reduction in BSA in our population, as very many of these prescriptions were given to vulnerable children including children with severe comorbidities. We therefor purpose more studies focusing on antibiotic use pattern in children with comorbidities including guideline assessments for these children.

Our definition of BSA was based on a governmental action plan published in 2015 [21]. In 2017, the WHO made a novel classification of antibiotics dividing them into three groups according to the potential of trigging resistance: Access, Watch and Reserve (referred to as the WHO AWaRe classification) [109]. The recent years, this classification has been applied in several antibiotic surveillance studies in children [56, 110]. For the future, national antibiotic stewardship goals and surveillance reports could benefit in applying the WHO AWaRe classification to cope with international surveillance.

5.3.2 Paediatric pneumonia

Pneumonia accounted for a higher proportion of the treatment indications at the DH (38%) compared to the UH (23%), and the difference was not affected by seasonal variation in the registration periods. All cases of pneumonia were community acquired.

Paediatric pneumonia is the most common indication for antibiotic treatment in-hospital, both in Norway [54] and worldwide [50, 52, 53, 55, 56, 103]. According to a study conducted at the same university hospital in Oslo from 2003 to 2005, 15/10 000 children 0-16 years in the uptake area were admitted for treatment of pneumonia per year [68]. In comparison, the corresponding incidence rates in our study of children 0-18 years were 16/10 000 at the DH and 7/10 000 at the UH. In a study from 2020, using the same recruited children from the DH (but excluding those with CF), only about half of the antibiotic treatments given for pneumonia complied with radiological, microbiological or laboratory criteria [111]. Supplemented by this latter study, we believe that the UH may had implemented a more strict practice of antibiotic use in children evaluated for pneumonia than the DH. Most cases of paediatric pneumonia are probably viral and do not need antibiotics [112, 113].

Total adherence rate to the Guideline was relatively high (72%), but only 52% for pneumonia, reflecting a large proportion of treatments involving other antibiotics than penicillin which is recommended in the Guideline [87]. Senstad et al. found that monotherapy with penicillin was used in 98% of reported cases of pneumonia (n =123) at the UH in the period 2003-2005, but children with a wide range of comorbidities were excluded [68]. According to a Norwegian study from 2016, *Streptococcus pneumoniae* remains the most frequent bacteria detected in children with pneumonia despite the introduction of vaccination programs [112]. The bacteria is in general susceptible to penicillin [18], although recent data indicate that a notable proportion of *S. pneumonia* isolates in children may require increased dose exposure [114, 115].

Internationally, an aminopenicillin is often recommended as first-line empirical choice for pneumonia [116, 117]. A Dutch study from a district hospital reported 48% adherence rate to amoxicillin [107]; another Dutch study from primary care revealed 75% adherence rate to amoxicillin in children 0-4 years of age and 54% adherence rate in children 12-17 years of age [58]. Two European studies found that adherence rate to an aminopenicillin was 71% in France [59] and 49% after an educational intervention in Italy [57].

We found that median number of days for in-hospital treatment of pneumonia was two days. In the pneumonia study conducted based on the same children from the DH, it was shown that median total treatment-length was 10 days, in line with current Norwegian guidelines (7-10 days) [87], but longer than recommended in a systematic review (3-7 days) [118].

5.3.3 Antibiotic dosing

We found wide variations in antibiotic dosing both within and between the hospitals. Specifically, median dose of ampicillin and cefotaxime was higher at the UH compared to the DH. Our results mirror that antibiotic dose guidelines vary substantially for many antibiotics, and that recommended dosing interval is wide within one single formulary, leaving clinicians to individual interpretations [64, 119, 120]. In 2021, Clements et al. investigated paediatric antibiotic dosing data from five global surveys [121]; in general, the authors found wide variations in dosing. Compared to our results, the most commonly used dosing for ampicillin was clustered around 200 mg/kg/day, and 83% of ampicillin doses were divided in 4 administrations (similar practice as in the UH).

Prudent dosing is essential to achieve the best possible clinical outcome, avoid toxicity, and avoid initiation of trigger mechanisms for developing resistance [65, 66, 122]. In 2019, Rashet et al. published a much needed systematic review including dose recommendations for 28 commonly used antibiotics based on available literature,

existing guidelines and clinical experience [122]. Most of the evidence was regarded intermediate or weak (92%).

In Norway, a modified version of the Dutch Kinderformularium, KOBLE, has been translated to Norwegian and is regarded the formulary of choice from 2021 [119] [120]. Here, the maximum recommended dose for amoxicillin/ampicillin IV for other infections than meningitis is 100 mg/kg/day divided in 3-4 administrations, indicating an overdosing of ampicillin in our population. For IV penicillin, KOBLE recommends from 60 and up to 240 mg/kg/day in severe cases; in our population median dose was around 100 mg/kg/day in both hospitals. One could question whether this dosing is too low as most children receiving IV penicillin have a potential severe infection. A Norwegian study reported that approximately 10% of *S. pneumonia* in invasive isolates required increased dose exposure of penicillin in children [115]. For oral penicillin, recommended dose in KOBLE is 50 mg/kg/day in moderate cases; in our population the median dose was slightly higher, about 60 mg/kg/day in both hospitals. In contrast, a systematic review recommended doses of IV penicillin in the range 80-100 mg/kg/day and doses of oral penicillin as high as 100-200 mg/kg/day. The rational for this drastic difference appears unclear [122].

5.4 Improving antibiotic use in hospitalised neonates (Paper 2)

At the DH, 358 neonates were admitted during 2017 whereof 95 (27%) were exposed to antibiotics, accounting for in total 685 prescriptions. At the UH, 235 neonates were admitted during the 4 month period in 2017 whereof 89 (38%) were exposed to antibiotics, accounting for in total 903 prescriptions. When merging the neonates from both hospitals together, the antibiotic exposure rate the first three days of life in term infants per total number of live born infants was 2.1%, while the corresponding proportion in premature infants (GA 28-36 weeks) was 12%. Antibiotic use rates in our study were low compared to studies from other countries [50, 55, 123-128], but in the same range as reported in Norway, nationally [81, 129]. A recently published study

conducted at one single hospital in western Norway reported a 57% relative reduction in term infants exposed to antibiotics within the first three days of life, from 2.9% in the period 2014-2016 to 1.3% in the period 2017-2018 [130]. Implementation of serial physical examinations was performed for the last period as a quality improvement initiative.

BSA accounted for only 4.3% of all prescriptions, a low proportion compared to surveys from other countries, even though the differences were not as drastic as for older children [55, 56]. In the following, I present three selected areas that we identified as important for future antibiotic strategies.

5.4.1 Unconfirmed cases of sepsis

Of all 91 EOS treatments in term infants, 23% were confirmed sepsis and 77% were unconfirmed sepsis. The number needed to treat for one positive blood culture was 46, and rose to 60 when including premature infants. Of all 30 EOS treatments in premature infants, none of these were confirmed sepsis. Of 52 sepsis treatments in extremely premature infants, 35% were confirmed sepsis, and the number needed to treat for one positive blood culture was four.

Two national registry studies conducted during the last decade also found high rates (54-71%) of neonates treated for unconfirmed infections shortly after birth [81, 129], but these studies did not evaluate CRP values. Thus, it is a strength that we have quality assured the inclusion criteria for culture-negative sepsis (CRP $\geq$ 30 mg/L, treatment $\geq$ 5 days [99]). However, the definition of culture-negative EOS varies between countries [131]. The concept of a culture-negative sepsis diagnosis has also been criticized, as blood cultures (if drawn properly) are very sensitive within 36-48 hours [83]. On the other hand, CRP values > 30 is not common in healthy term born infants [132].

Our results indicate low threshold for antibiotic therapy in premature infants. A randomized controlled study from India including premature infants with GA 27-36 weeks concluded that routine antibiotics after birth did not have any protective role in infants with low risk [133]. The high rates of positive blood cultures that we found in

extremely premature infants is also mirrored elsewhere [134]. This emphasizes to call for strategies to reduce the burden of infections in neonatal departments, such as demonstrated by Neill et al. [135]. On the other hand, antibiotic use in premature infants is associated with decreased bacteria diversity in the gut [27], and with severe early adverse outcomes such as death and necrotizing enterocolitis [37, 38]. The latter is debated, and a recent multi-centre cohort study found that neonates < 1500 gram who were not given antibiotics the first days of life had increased risk of necrotizing enterocolitis [136]. Thus, navigating the balance between efficient infection care and antibiotic stewardship in extremely premature infants is challenging. A systematic review called for more antibiotic stewardship efforts in premature infants.[137]

Based on the high number of unconfirmed sepsis episodes in our population, there is certainly a potential for reduction in antibiotic exposure rates. Interventions such as serial physical examinations or risk algorithms could be initiated to safely reduce antibiotic exposure [124, 130]. Increased focus could be targeted towards premature infants, but in those with GA < 28 weeks, attention should mainly be focused towards early discontinuation of antibiotics and prevention of infections.

5.4.2 Treatment-length in unconfirmed cases of sepsis

Mean treatment length for unconfirmed EOS was 3.0 days both in term infants and in premature infants. For extremely premature infants, mean treatment length for unconfirmed sepsis (EOS or LOS) was 4.3 days.

Fjalstad et al. revealed a median treatment length of four days for unconfirmed cases of EOS in term infants nationally in 2009-2011 [81], while Dretvik et al. reported a median treatment length of 48 hours in unconfirmed cases after the implementation of a guideline to stop antibiotics within 36-48 hours [138]. Interventional studies from other countries have reported that an automatic 48-hour antibiotic stop order safely reduced antibiotic use [123, 139], also in extremely premature infants [140]. Several reviews, as well as the Guideline, recommend discontinuing antibiotic treatment if blood cultures remain negative after 36-48 hours if clinical symptoms are mild and biomarkers show

low values [83, 87, 131]. We suggest to implement strategies such as 36-48 hour automatic stop order in our study hospitals or simply find local strategies to increase the awareness to the updated clinical guideline [87].

5.4.3 Choice and dose of aminoglycosides

Tobramycin was the aminoglycoside of choice at the DH while gentamicin was preferred at the UH. This difference is also seen among countries in Western Europe [55]. It has been investigated whether gentamicin is more nephrotoxic than tobramycin, but there are no certain reasons to believe so [141, 142]. Tobramycin is preferred in treatments of infections caused by *P. aeruginosa*, but this pathogen is rarely detected in the Norwegian neonatal population [81, 115, 129]. Tobramycin is more expensive than gentamicin, favoring the use of gentamicin.

For term infants treated with antibiotics the first week of life, median aminoglycoside doses were higher at the UH (6 mg/kg/day) than at the DH (5 mg/kg/day). The difference of aminoglycoside dosing in neonates is also reflected in guidelines; 6 mg/kg/day is recommended in the Guideline [87], while Rashed et.al recommended 5 mg/kg/day in a systematic review of doses [122]. Studies have shown that using 6 mg/kg/day is safe according to the measured plasma concentration of the drug, ototoxicity and long-term nephrotoxicity [142-144]. As for children, there is a need for national and international consensus of dose regimes in neonates [118].

5.5 Ambulatory antibiotic use in children (Paper 3)

5.5.1 Selected main results

In total, 187 children in the H+ group received antibiotics at the DH during 2017, corresponding to 3.7 per 1000 children in the catchment area.

In the H+ group, 44% received antibiotics in ambulatory care during the year before hospitalisation and 46% during the year after hospitalisation, compared to 15% before and 17% after hospitalisation in the H- group, RR 2.9 (95% CI 2.4-3.5) before and 2.8 (2.3-3.3) after hospitalisation, comorbidity adjusted RR 2.3 (1.8-2.9) before and 2.3 (1.8-2.8) after hospitalisation. The IRR for total number of prescriptions in the H+ group compared to the H- group was 6.8 (95% CI 5.0-9.3) before and 6.1 (4.4-8.3) after hospitalisation, comorbidity adjusted IRR 4.0 (3.0-5.3) before and 4.4 (3.0-6.6) after hospitalisation. We revealed no significant differences in the RR or IRR before and after hospitalisation, but a slightly trend towards lower RR and IRR after hospitalisation for most subgroups. Of all 295 ambulatory prescriptions in the H+ group, 45 (15%) were macrolides and 81 (27%) were certain predefined oral broad-spectrum antibiotics.

5.5.2 Discussion

The approach that we have used to study connections between in-hospital and ambulatory antibiotic use is novel and original. Attention to recurrent users of antibiotics has been particularly highlighted as an important part of antibiotic stewardship programs [71]. The increased risk of ambulatory antibiotic use in the H+ group is not surprising itself, as this is a selected group of children with a wide range of comorbidities. However, it was interesting to reveal how high this risk was also after comorbidity adjustment. Complicated infections with resistant bacteria could possibly occur and lead to multiple antibiotic prescriptions not captured by our comorbidity methods, but antimicrobial resistant rates in Norway are in general low [112], and in paper 1 we reported very few cases of hospital-acquired infections, as well as positive blood cultures. The increased risk of ambulatory antibiotic use for the H+

group was relatively equal regardless of the indication for antibiotic treatment in-hospital, treatment length and antibiotic choice (BSA). Thus, we could not sort out a specific group requiring particular attention. In paper 1 we found a large amount of children treated for pneumonia at the DH and did further investigations in another paper whether all these treatments were appropriate [111]. In this paper (paper 3), we found that 50-60% of these patients were prescribed antibiotics both before and after hospitalisation.

The risk of antibiotic use for the H+ group was not increased during the year after hospitalisation compared to the year before; instead, the risk was high both before and after hospitalisation, also after comorbidity adjustment. This suggests that other reasons than underlying medical conditions contributed to the increased risk. We suspect that behavioural, cultural and psychological factors in children and parents could be relevant, such as language barriers, long-term illnesses in parents and generally poor reliability of caregivers [77, 78, 91]. These factors could potentially create a selection of children who more often are in contact with health-care staff, and thus in increased risk of receiving antibiotics in ambulatory care. Once frequent antibiotic use in primary care is established, the risk of side effects, antimicrobial resistance and treatment failure also increase which itself could lead to hospitalisation. This could potentially create a cycle of antibiotic exposure that is hard to break out off.

Our study hospital did not have a specific antibiotic stewardship program for children, even though this is recommended in all paediatric departments [145]. Moreover, the focus in hospitalised children has been directed towards antibiotic use during hospitalisation only, as data often derive from reports describing in-patient use. We purpose that hospitalisation could give an opportunity to go through antibiotic prescription history, if appropriate together with the parents. By doing this, one could tailor an upcoming plan for the threshold of antibiotic use as well as preferable choices of antibiotics. In Norway, children have their own general practitioner; a closer collaboration and information-flow between hospitals and general practitioners could be valuable in communicating aspects of antibiotic use in the transmission between hospitalisation

and ambulatory care. We encourage more studies to further examine the reasons for the high ambulatory antibiotic use rate in children who have received antibiotics in–hospital.

Use of macrolides and certain oral broad-spectrum antibiotics (co-trimoxazole, clindamycin, cephalexin, ciprofloxacin) was relatively high in the H+ group. These antibiotics are not first-line recommendations in the Guideline [87]. However, oral paediatric formulations of narrow-spectrum first-line antibiotics such as piv-mecillinam and dicloxacillin/flucloxacillin are not available for sale on the Norwegian marked. Moreover, the paediatric liquid formulation of penicillin has a poor taste [146, 147]. This may have contributed to the relatively high use of the above mentioned antibiotics. For the future, one should work for increased availability of child-friendly oral formulations of all antibiotics recommended in the Guideline. This work has to be conducted through a cooperation between medical professionals, researchers, politicians and the pharmaceutical industry.

5.6 Ambulatory antibiotic use in infants (paper 4)

5.6.1 Main results

In total, 95 infants were included in the AB+ group and these were matched with 950 infants from the general infant population (AB- group).

Of all infants in the AB+ group, 23% were re-exposed to antibiotics in ambulatory care during the following year compared to 14% use in the AB – group, RR 1.7 (95% CI 1.1-2.5), comorbidity adjusted RR 1.4 (0.9-2.2). Only 5% of the infants in the AB+ group received oral broad-spectrum antibiotics during the following year. In low-risk AB+ infants (n=62), 27% received antibiotics during follow-up compared to 11% in the AB- group, comorbidity adjusted RR 2.1 (1.3-3.7). In preterm AB+ infants (n=25), only 12% received antibiotics during follow-up.

IRR for total number of prescriptions in the AB+ group compared to the AB- group was 2.8 (95% CI 1.6-4.9), comorbidity-adjusted IRR 1.4 (0.8-2.5). When including one prescription per type of antibiotic per infant, penicillin accounted for 48% of the prescriptions in the AB+ group and for 47% of the prescriptions in the AB- group.

5.6.2 Discussion

In paper 2, we showed that the wide majority of infants treated for suspected sepsis were not likely to have an infection. Despite this, the incidence of invasive infections is much higher in infants compared to older children [79, 80, 115]. The other aspect one has to consider is how antibiotic exposure may alter and harm the immature microbiome in these infants, which again can disturb the function and cooperation with the immunologic and metabolic system [24, 27-29]. This may increase the risk for various chronical conditions [29-36], but one has to consider that most of these studies are observational including various confounders. One small randomized controlled trial failed to demonstrate that early antibiotic administration to premature infants after birth altered the microbiome [148].

Our study was observational and explorative and was not designed to conclude the causality for the increased risk that we observed. However, we aimed to investigate certain risk factors as they might by indicative of possible causal factors. Comorbidity adjustments decreased the RR slightly in all analyses. In the main analyses for all infants, RR and IRR decreased to a non-significant level indicating that these comorbidities were of importance. Pyelonephritis was the single most identifiable risk factor for recurrent use. It is known that urinary tract infections in small children often relapse and use of prophylactic antibiotics is common [89, 149].

Surprisingly, very few premature infants in the AB+ group were re-exposed to antibiotics. We speculate that these infants were more protected from the environment after hospitalisation, and thus had lower risk of infections. In addition, as stated in paper 2, none of the premature infants (GA 28-36) treated for suspected EOS had a confirmed infection, lowering the probability of infection-related comorbidities.

However, these findings should be interpreted with some caution, as the sample size in this subgroup was rather small with wide confidence intervals.

The low-risk infant subgroup was established to mirror a close to normal infantile population removing those with severe neonatal complications and risk of prolonged hospitalisation. These infants had more than double risk of recurrent antibiotic use, also after comorbidity adjustment. We speculate that behavioural or psychological factors could be an important factor in explaining the increased risk of recurrent use for this group; in a cohort of Finish children, the authors found that long-term illnesses in parents, the father`s need for outside support, infantile colic and frequent use of medical care all were associated with recurrent use of antibiotics up to the age of 18 months [90, 91]. Hospitalisation itself was also found to be an independent risk factor [90]. Another study reported that hospitalisation of children led to increased stress in parents [76]. We wonder if treatment for a suspected severe infection in early childhood may have worried the parents lowering the threshold for visiting a doctor, ending up with an antibiotic prescription for a self-limiting respiratory tract infection. Also, prescriber`s attitudes to ambulatory antibiotic prescribing in small children could be influenced by a history of early treatment for a possible severe infection [78]. Thus, it is important that the family gets adequate information at discharge and are reassured in cases were no infection is likely. Information regarding the possible negative consequences of antibiotics in early childhood could be informative for both parents and outpatient clinics.

6. Conclusions

We examined different aspects of antibiotic use in a cohort of hospitalised children and neonates before, during and after hospitalisation. All-over, we found no major differences in main aspects of antibiotic use pattern between the UH or DH; adherence to the Guideline was relatively high and use of BSA was low in both hospitals. We have highlighted several potential areas for future antibiotic stewardship in both children and neonates admitted to hospitals; also, we found an association between antibiotic use during hospitalisation and increased use of antibiotics in ambulatory care before and after hospitalisation compared to the general paediatric and infant population.

1. **Antibiotic use in hospitalised children:** Agreement on dosing, pneumonia-treatments (threshold for treatment and antibiotic choice) and evaluation of BSA use in children with comorbidities should be important aspects in paediatric antibiotic stewardships programs in hospitalised children in our population.

2. **Antibiotic use in hospitalised neonates:** Choice and dosing of aminoglycosides, safely reduction of antibiotic exposure rates for suspected sepsis and safely reduction of treatment length in unconfirmed sepsis should be important aspects in neonatal antibiotic stewardship programs in our population.

3. **Ambulatory antibiotic use in children:** Antibiotic use during hospitalisation in children was associated with increased use of antibiotics in ambulatory care both before and after hospitalisation compared to the general paediatric population, but the risk of receiving antibiotics did not change after hospitalisation compared to before hospitalisation.

4. **Ambulatory antibiotic use in infants:** Receiving antibiotics during the first three months of life was associated with increased use of antibiotics in ambulatory care during the following year compared to the general infant population.

7. Further perspectives

7.1 Antibiotic use during hospitalisation

We have conducted prospective registrations of clinical data. This was informative, and optimally all paediatric and neonatal wards should aim for period registrations of antibiotic use from time to time. However, data collection is resource demanding. Electronic medical prescribing systems have become more widespread in Norwegian hospitals the recent years and may simplify antibiotic surveillance in the future, especially if one can connect prescribed drug with an indication for use and achieve ethical approvals that can facilitate the use of such data. A recent published study from the UK is promising in terms of using such data in hospitalised children [104].

It is tempting to focus on areas of improvement only, but I also believe that documentation of rational practice of antibiotics itself is important; it could motivate other countries towards a rational shift in antibiotic use. In this context, it is important to mention that we revealed low antibiotic use rates compared to other countries. Thus, the data from our study should be used actively in presentations and discussion with researchers, medical doctors and decision makers from other countries.

For neonates, we suggested that future interventions to reduce both antibiotic exposure rates and treatment length in unconfirmed infections could be considered in both of our study hospitals. Recently, studies from other hospitals in Norway have reported a favourable outcome of such interventions in term and late-preterm infants. However, intervention efforts in preterm infants less than 34 weeks is lacking and should be prioritized. Also, we need more information on the potential harmful effect to the microbiome, as the severity of this will guide the goal for how drastic one should aim for antibiotic reduction in neonates. Finally, after our study, the DH changed their recommendations in choice and dose of aminoglycosides and started to recommend penicillin instead of ampicillin for suspected EOS, to cope with recent knowledge and national guidelines [87].

In the Norwegian action-plan for antimicrobial resistance, reduction of BSA in hospitals is one of the major aims [21]. To target whether BSA use in hospitalised children can be safely reduced, I think future investigations are needed assessing guidelines and practice in children with comorbidities specifically. Also, we need reports from specialized wards treating oncological patients and children with severe immunodeficiencies, as these certainly use more BSA [69]. Based on the large difference in the number of children treated for suspected pneumonia and the high use of other antibiotics than penicillin in the treatment, I suggest that a unified agreement in selecting appropriate patients for antibiotic treatment and further understanding in the choice of non-penicillin antibiotics should be of high priority in paediatric antibiotic stewardship in Norway. I suspect such variations to be present nationally. An ongoing randomized controlled study comparing amoxicillin with placebo in paediatric pneumonia will hopefully give some clarifying answers regarding the role of antibiotics for this indication [150].

Even though there is a lack of evidence partly explaining the variation of doses that we observed, I think it would be useful to aim for a more tangible national (and international) consensus of antibiotic dose choices, also for future research purpose. The difference in the rate of blood culture obtainment between the hospitals could desirable be followed up by a national consensus regarding the threshold for obtaining blood cultures for various infections. Currently, there is an ongoing national discussion regarding empirical antibiotic recommendations for sepsis or suspected sepsis in adults [151]. This discussion is also important in children, and I do question whether the current recommendation (ampicillin plus an aminoglycoside) has adequately coverage for *Staphylococcus aureus* [115].

7.2 Antibiotic use in ambulatory care before and after hospitalisation

The investigation of the connection between antibiotic use during hospitalisation and in ambulatory care is novel and may help in achieving a more holistic picture of paediatric antibiotic use. It should motivate future studies that could target reasons for increased ambulatory use in the hospitalised group with more depth such as including variables on sociodemographic factors in parents and in prescribers in ambulatory care. I suggest that being hospitalised is a good opportunity to perform an evaluation of all-over antibiotic use on an individual level including relevant information to parents as well as tailoring an upcoming plan regarding threshold and choice of antibiotics.

In infants, avoiding inappropriate recurrent antibiotic use is particular important given their immature microbiome and possible risk of long-term negative health outcomes. In general, it is desirable with more studies targeting ambulatory antibiotic use during the first year of life, and potential interventions could include information audits to prescribers and parents, and that adherence to guidelines is particular important for this age group. Finally, pushing the pharmaceutical industry to produce and deliver paediatric formulations of recommended oral antibiotics is important; to achieve this I think governmental help and economical support is needed as there are no economical incentives for the pharmaceutical companies to produce and sale small amounts of antibiotics to a small country like Norway.

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Paper I

BMJ Open

Using a period incidence survey to compare antibiotic use in children between a university hospital and a district hospital in a country with low antimicrobial resistance: a prospective observational study

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ABSTRACT

Objectives To describe and compare antibiotic use in relation to indications, doses, adherence rate to guidelines (BSA) and rates of broad-spectrum antibiotics (BSA) in two different paediatric departments with different academic cultures, and identify areas with room for improvement.

Design Prospective observational survey of antibiotic use.

Setting Paediatric departments in a university hospital (UH) and a district hospital (DH) in Norway, 2017. The registration period was 1 year at the DH and 4 months at the UH.

Participants 201 children at the DH (mean age 3.8: SD 5.1) and 137 children at the UH (mean age 2.0: SD 5.9) were treated with systemic antibiotics by a paediatrician in the study period and included in the study.

Outcome measures Main outcome variables were prescriptions of antibiotics, treatments with antibiotics, rates of BSA, median doses and adherence rate to national guidelines.

Results In total, 744 prescriptions of antibiotics were given at the UH and 638 at the DH. Total adherence rate to guidelines was 75% at the UH and 69% at the DH (p=0.244). The rate of treatments involving BSA did not differ significantly between the hospitals (p=0.263). Use of BSA was related to treatment of central nervous system (CNS) infections, patients with underlying medical conditions or targeted microbiological treatment in 92% and 86% of the treatments, at the UH and DH, respectively (p=0.217). A larger proportion of the children at the DH were treated for respiratory tract infections (p<0.01) compared with the UH. Children at the UH were treated with higher doses of ampicillin and cefotaxime (p<0.05) compared with the DH.

Conclusion Our results indicate that Norwegian paediatricians have a common understanding of main aspects in rational antibiotic use independently of working in a UH or DH. Variations in treatment of respiratory tract infections and in doses of antibiotics should be further studied.

Strengths and limitations of this study

► This paediatric study is based on individual patient data collected prospectively in a university hospital and a district hospital in a country with low antimicrobial resistance and includes information on antibiotic use, indications for treatment, underlying medical conditions, microbiological samples and doses.

► No registration data were missing on the included children.

► The adherence rate to the national antibiotic guideline for common infections was calculated.

► Some case-mix differences in the two study populations made us carefully select outcomes that was comparable.

INTRODUCTION

Antimicrobial resistance (AMR) represents a serious threat to global health and is partly caused by inappropriate use of antibiotics.[1–3] Exposure to antibiotics, especially broad-spectrum antibiotics (BSA) in children, may also increase the risk of various chronic diseases.[4–6] Use of BSA in Norwegian hospitals have increased during the last 10 years despite low resistance rates.[7 8] Norway has a National Strategy against AMR including a 30% reduction in the use of BSA in hospitals within 2020[9]

Raastad *et al* revealed a significantly increased consumption of BSA in a highly specialised Norwegian paediatric department.[10] Our group recently showed that a high number (30%) of children in Norwegian general hospitals are receiving BSA,[11] and that adherence rate to antibiotic guidelines is low (48%). However, parameters such

Table 1 Empirical recommendations for treatment of infections in Norwegian children

Indication	First-line empirical recommendation in the guideline*
Pneumonia	► Phenoxymethylpenicillin or benzylpenicillin
Urinary tract infection	► Aminoglycoside plus ampicillin ► Pivmecillinam or amoxicillin/clavulanic acid
Sepsis and neutropenia	► Aminoglycoside plus ampicillin
Infections in skin, soft tissue, bone and joint	► Cloxacillin, dicloxacillin, clindamycin, cefalotin, cefalexin, phenoxymethylpenicillin or benzylpenicillin (alone or in combination)
Infection in ear, eye and throat	► Phenoxymetylpenicillin or benzylpenicillin (throat and ear) ► Cefotaxime or clindamycin (severe infections)
CNS infections	► Cefotaxime or ceftriaxone

*First-line treatment options in the Norwegian guideline.[28]
CNS, central nervous system.

as underlying medical conditions, treatments based on microbiological samples and doses of antibiotics were not evaluated.

Differences in antibiotic prescription patterns for paediatric inpatients are observed between countries,[12 13] and also within geographical areas.[14–17] A low adherence rate to paediatric antibiotic guidelines is a global challenge both in hospitals and primary care, and especially in respiratory tract infections.[18–20] Furthermore, there is no common international agreement regarding the optimal antibiotic dose for children in relation to body mass and type of infection.[13 21–24] In fact, scientific evidence does not give a clarifying answer on whether a higher or a lower dose of antibiotics will minimise the development of antibiotic resistance,[25] but the mutant selection window theory indicate the importance of a high enough dose.[26]

In Norway, all acute care hospitals are public. There are 68 hospitals registered in the database of The Norwegian Institute of Public Health; 6 of these are university hospitals (UHs), while the remaining are smaller district hospitals (DHs). Twenty-three of the hospitals have a paediatric department. Comparing hospitals of different sizes and academic cultures gives a more valid description of antibiotic prescriptions throughout the country. The UHs are holding many academic positions and are expected to be role models in clinical practice for the DHs. We therefore speculate if there are any clearly differences in pattern of antibiotic use in children between centrally located UHs and more rural located DHs.

The primary aim of this study is to investigate whether use of BSA and adherence rate to antibiotic guidelines differs between children treated in a centrally located UH and a more rural located DH. The secondary aim is to compare the distribution of indications for treatment, the duration of hospital treatment, route of administration, use of combination therapy, obtaining rate of blood cultures and doses of antibiotics. All aims are seen in the context of targeting areas for improvement of antibiotic use.

METHODS
Study setting and design
This is a prospective study using a period incidence design to compare paediatric antibiotic prescriptions in a UH (Oslo University Hospital, Ullevål) and a DH (Ålesund Hospital) in Norway, 2017. Neonatal and paediatric intensive care units were not included. In both hospitals, children 0–18 years of age are admitted in paediatric departments.

Hospitals
Ålesund Hospital, hereafter called the DH, is located in the western part of Norway, and holds a wide range of medical specialty services. The paediatric ward consists of 18 beds. Data were collected during 12 months in 2017, from 1 January to 31 December.

The paediatric department in Oslo University Hospital, Ullevål (UH) consists of various wards. We collected data from the paediatric infectious ward (18 beds) during 4 months in 2017, from 1 June to 31 July and from 17 October to 17 December. In the period from 1 to 31 July, the general paediatric ward was merged with the paediatric infectious and observation ward because of summer holiday and included in our registration.

The UH is a national referral centre for children with cystic fibrosis, but does on the other hand not admit oncological or cardiological patients. The DH does not have any national services, but treat children with all kinds of clinical conditions. In opposite to the DH, the UH has many paediatricians holding academic positions working in close collaboration with the clinicians.

Data collection
The data were collected from the medical records every day at 08:00 in both hospitals. In the DH, this was done by trained nurses working on the ward and double-checked by a medical doctor every day. In the UH, one paediatrician did all registrations, and the quality control was performed by the head of this project. For registrations, we applied an international standardised point prevalence protocol developed by the European Centre for Disease Prevention and Control (ECDC),[27] and the data were stored in an electronical database (without national identification numbers). Educational classes to doctors and nurses who were data collectors were held before the start of registration in both hospitals.

Data collection included the total number of patients in the wards, national identification numbers, gender, age, weight, underlying medical conditions, type and

Table 2 Antibiotic prescriptions by paediatricians for treatment of infections in a Norwegian university hospital and a district hospital (only in-hospital prescriptions)

	Total	University hospital	District hospital	P value*
Bed days				
Children in hospital uptake area		137233	50274	
Bed days, n	3844	1833	2011	
Bed occupancy rate, %	73	83	44	<0.01
Bed days with antibiotics, n (%)	1058 (28)	524 (29)	534 (27)	N/A†
Bed days with antibiotics/100 children in uptake area	1.12	1.15	1.06	N/A†
Prescriptions				
Prescriptions, n	1382	744	638	
Intravenous prescriptions, n (%)	992 (72)	613 (82)	379 (59)	<0.01
Monotherapy, n (%)	672 (49)	284 (38)	388 (61)	<0.01
BSA‡, n (%)	269 (20)	172 (23)	97 (15)	0.03
Total administered doses/100 bed days	36	41	31	N/A†
Patients				
Total, n	338	137	201	
Male/female (%)	52/48	58/42	47/53	NS
Age in years, mean (SD)	3.0	2.0 (5.9)	3.8 (6.1)	NS
Weight in kg, median (IQR)	14.0 (22.1)	13.0 (25.1)	15.4 (20.0)	NS
Days of treatment in hospital, median (IQR)	2.0 (3.0)	3.0 (3.0)	2.0 (2.0)	<0.01
Treatment for >1 indication	7 (2)	5 (4)	2 (1)	N/A
Comorbidity, n (%)	118 (35)	46 (34)	72 (36)	NS

*A χ^2 test was used for proportions, Student's t-test for means and Moods median test for medians.
†In the district hospital, all paediatric bed days were included, but in the university hospital only those admitted to the infectious ward were included. A statistical comparison of total antibiotic use was therefore not performed.
‡Broad-spectrum antibiotics (BSA): second-generation and third-generation cephalosporins, carbapenems, piperacillin/tazobactam, carbapenems and ceftolazan/tazobactam. P-value < 0.05 was regarded significant.

dose of antibiotics, route of administration, whether it was for treatment or prophylaxis, indication for antibiotic treatment and whether the infection was healthcare or community acquired. Results from blood cultures, bone/joint aspirations and airway samples from patients with cystic fibrosis were registered.

Definitions

Definitions of underlying medical conditions and the clinical indication for treatment derived from the ECDC rules for conducting a point-prevalence survey[27] and were reported based on predefined lists. Less severe medical conditions such as allergies and asthma without daily medication were not registered as comorbidities. Surgical prophylaxis was defined as antibiotics given immediately before, during or shortly after surgery to prevent infection. Medical prophylaxis was defined as antibiotics prescribed to prevent infection in patients at risk. Healthcare-associated infections were defined according to the ECDC criteria.[27] Antibiotics were defined as antibacterials for systemic use (J01), oral vancomycin (A07AA09) and oral metronidazole (P01AB01). Tuberculostatics (eg, rifampicin) were not included. BSA were defined as

second-generation and third-generation cephalosporins, ceftolozane/tazobactam, carbapenems, piperacillin/tazobactam and quinolones, according to the National Strategy against AMR.[9]

Guidelines

To evaluate adherence to guidelines, we used empirical recommendations given in Norwegian Guidelines—Acute Paediatrics by The Norwegian Pediatric Association.[28] Treatments in accordance with susceptibility patterns from blood cultures, bone/joint aspirations and airway samples in patients with cystic fibrosis were also included when calculating the adherence rate. A summary of the empirical recommendations is shown in table 1.

An adherence rate of at least 65% was regarded as satisfactory based on our previous study.[11] When evaluating doses of antibiotics, we used the British National Formulary for Children,[29] because it is commonly used by Norwegian paediatricians. We did not evaluate whether treatment with antibiotics was indicated in the first place, nor the length of the treatment, only choices of antibiotics and doses.
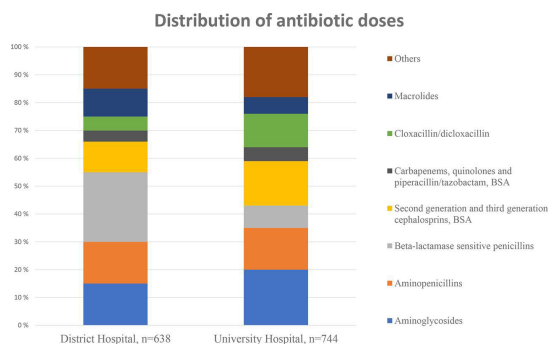
Distribution of antibiotic doses

Figure 1 Distribution of antibiotic doses given by paediatricians for treatment of infection to hospitalised children in a Norwegian district hospital and a university hospital. Broad-spectrum antibiotics (BSA) and all other antibiotics accounting for >10% of total doses in one of the hospitals were included.

Analyses

To minimise case-mix variations between the hospitals, only admissions of patients treated by paediatricians (not surgeons) and antibiotics issued for treatment of infections (not prophylaxis) were included in our analyses. Antibiotic use was described in relation to bed days, total number of antibiotic prescriptions, proportion of admitted patients receiving antibiotics and the total number of antibiotic treatments. One prescription was defined as a daily dose with one antibiotic, and treatment was defined as antibiotic therapy for a certain indication in a certain time range. Doses were described and compared in mg/kg/day only for children <40 kg, and we controlled for hospital differences in distribution of indications and weight by doing stratified analyses. When comparing adherence rate to guideline and BSA use we adjusted for age. We also controlled for the impact of seasonal variation by analysing data on treatments with identical registration periods.

Statistics

Statistical analyses were performed using Microsoft excel 2016 and SPSS Statistics V.23. The proportion of children receiving antibiotics was described separately for each hospital without statistically comparisons because of case mix. For all other analyses including BSA rates (%), comorbidity rates (%), age (mean), duration of treatment (median), doses (median) and route of administration (%), comparisons were done using either χ^2 test (proportions), Student's t-test (means) or Moods median test (medians). Fishers exact test was used to analyse differences in distribution of indications when comparing doses. When comparing adherence to guidelines and use of BSA, we controlled for age differences between the hospitals by using a multivariable logistic regression analyse adjusting for age as an independent variable. A p<0.05 was considered significant. SD was used in relation

to means and IQR in relation to medians. No data were missing for the statistical analyses.

Patient and public involvement

This study is part of a comprehensive project, 'Born in the sunset of antibiotics—use of antibiotics in hospitalized children in a country with low antimicrobial resistance'. For this project, we have recently recruited a user representative from The Norwegian Society of Children's Cancer. She has received the project protocol, but not been directly involved in the conduction of this specific study; however, she will help implement our results to the general population and take more actively part in upcoming studies.

RESULTS
General demographics

In total, 3844 bed days (1833 at the UH and 2011 at the DH) were registered, whereof 28% (29% at the UH and 27% at the DH) included exposure to antibiotic therapy (table 2).

The proportion of intravenous infusions and combination of antibiotics were significantly higher at the UH compared with the DH (p<0.01). Thirty-four per cent of patients at the UH and 36% at the DH had an underlying medical condition. No fatalities were registered during the study periods.

Total antibiotic use

Beta-lactamase susceptible penicillins accounted for the highest proportion (25%) of antibiotic prescriptions at the DH compared with 8% at the UH (p<0.01). Aminoglycosides represented the highest proportion (20%) at the UH compared with 15% at the DH (figure 1).

Indications for treatment with antibiotics and adherence rate to the guideline

Of all 345 treatments, 32% where given for pneumonia (table 3). At the DH, a higher proportion of treatments were given for pneumonia (p<0.01) and upper respiratory tract infections (p<0.01) compared with the UH, while more patients at the UH were treated for infections in skin, soft tissue, bone and joint (p<0.01). For infections in skin, soft tissue, bone and joint, 9 (27%) out of 33 treatments at the UH and 10 (43%) out of 33 treatments in the DH involved clindamycin (p=0.176). Total adherence to guideline was 72%, varying for different indications, and without significant differences between hospitals (table 3). Treatments for pneumonia had the lowest adherence rate to the guideline; 25% of the treatments involved erythromycin at the UH and 18% at the DH; 13% of the treatments involved aminopenicillins or trimethoprim–sulfamethoxazole at the UH and 15% at the DH.

Use of BSA

The proportion of treatments involving BSA varied for different indications, but we revealed no significant

Table 3 Paediatric antibiotic prescriptions for different indications in a Norwegian university hospital and a district hospital

Indications for antibiotic treatment	Total	University hospital	District hospital	P value*
All indications†				
Treatments, n	345	142	203	
Healthcare-acquired infections, n (%)	17 (5)	11 (8)	6 (3)	*0.04*
Treatments involving BSA‡, n (%)	72 (21)	34 (24)	38 (19)	NS
Treatments according to guideline§¶, n (%)	232 (72)	96 (75)	136 (69)	NS
Pneumonia				
Treatments, n (% of all treatments)	110 (32)	32 (23)	78 (38)	*<0.01*
Treatments involving BSA, n (%)	24 (22)	11 (34)	13 (17)	NS
Treatments according to guideline, n (%)	57 (52)	15 (47)	42 (54)	NS
Days of treatment in hospital, median (IQR)	2.0 (3.0)	3.0 (4.5)	2.0 (2.3)	NS
Treatments to patients with comorbidities, n (%)	54 (49)	19 (59)	35 (45)	NS
BSA treatments to patients with comorbidities**, n (% of BSA)	23 (96)	11 (100)	12 (92)	NS
Urinary tract infection				
Treatments, n (% of all treatments)	59 (17)	28 (20)	31 (15)	NS
Treatments involving BSA, n (%)	6 (2)	2 (7)	4 (13)	NS
Treatment according to guideline, n (%)	50 (85)	26 (93)	24 (77)	NS
Days of treatment in hospital, median (IQR)	2.0 (2.0)	2.0 (1.8)	3.0 (3.0)	NS
Treatments to patients with comorbidities, n (%)	20 (34)	7 (25)	13 (42)	NS
BSA treatments to patients with comorbidities, n (% of BSA)	5 (83)	2 (100)	3 (75)	N/A
Infection in skin, soft tissue, bone and joint				
Treatments, n (% of all treatments)	56 (16)	33 (23)	23 (11)	<0.01
Treatments involving BSA, n (%)	8 (14)	6 (18)	2 (9)	NS
Treatments according to guideline, n (%)	41 (73)	23 (70)	18 (78)	NS
Days of treatment in hospital, median (IQR)	2.0 (4.0)	3.0 (5.0)	1.5 (3.0)	NS
Treatments to patients with comorbidities, n (%)	10 (18)	1 (3)	9 (38)	*<0.01*
BSA treatments to patients with comorbidities, n (% of BSA)	1 (10)	0 (0)	1 (50)	N/A
Sepsis				
Treatments, n (% of all treatments)	34 (9)	19 (13)	15 (7)	NS
Treatments involving BSA, n (%)	7 (21)	4 (21)	3 (20)	NS
Treatments according to guideline, n (%)	30 (88)	18 (95)	12 (80)	NS
Days of treatment in hospital, median (IQR)	3.5 (4.0)	3.0 (3.0)	5.0 (5.0)	NS
Treatments to patients with comorbidities, n (%)	14 (41)	8 (42)	6 (40)	NS
BSA treatments to patients with comorbidities, n (% of BSA)	6 (86)	3 (100)	3 (75)	N/A
Upper respiratory tract infections				
Treatments, n (%)	42 (12)	7 (5)	35 (17)	*<0.01*
Treatments involving BSA, n (%)	2 (5)	1 (14)	1 (3)	NS
Treatments according to guideline, n (%)	34 (81)	7 (100)	27 (77)	NS
Days of treatment in hospital, median (IQR)	2.0 (2.0)	2.0 (2.0)	2.0 (2.0)	NS
Treatments to patients with comorbidities, n (%)	10 (24)	2 (29)	8 (23)	NS
BSA treatments to patients with comorbidities, n (% of BSA)	1 (50)	1 (100)	0 (0)	N/A
CNS infections				
Treatments, n (%)	23 (7)	9 (6)	14 (7)	NS
Treatment involving BSA, n (%)	20 (87)	7 (78)	13 (93)	NS
Treatments according to guideline, n (%)	20 (87)	7 (78)	13 (93)	NS

Continued

Table 3 Continued

Indications for antibiotic treatment	Total	University hospital	District hospital	P value*
Days of treatment in hospital, median (IQR)	1.0 (2.0)	2 (3.0)	1 (1.25)	NS
Treatments to patients with comorbidities, n (%)	1 (4)	1 (11)	0 (0)	NS
BSA treatments to patients with comorbidities, n (% of BSA)	1 (5)	1 (14)	0 (0)	NS
Other infections				
Treatments, n (%)	21 (6)	14 (10)	7 (3)	*0.03*
Treatments with BSA, n (%)	5 (24)	3 (21)	2 (29)	NS

*A χ^2 test was used for proportions and Moods median test for medians. Non-significant results are marked NS. N/A means that the numbers are too small for statistical testing.

†For adherence rate and BSA use, we controlled for age differences between the hospitals by using multivariable logistic regression, and the significant levels remained the same for all indications. P-value < 0.05 was regarded significant.

‡Broad-spectrum antibiotics (BSA) were defined as second-generation and third-generation cephalosporins, carbapenems, piperacillin/tazobactam and ceftolazan/tazobactam.

§The entire treatment is in adherence with the empirical recommendation in The Norwegian guideline[28] *and/or* in accordance with blood cultures, bone/joint cultures or respiratory tract samples from cystic fibrosis patients (means using any antibiotic(s) that was susceptible by the bacteria, regardless of how the patient was treated initially).

¶Other infections were not included when calculating total compliance with guidelines.

**University hospital: cystic fibrosis with pathogenic bacteria (9), cerebral palsy (1), recent CNS operation (1), district hospital: cystic fibrosis with pathogenic bacteria (8), lymphoma (1), neurological multifunction disability (1), heart disease (1), syndrome (1).

CNS, central nervous system.

differences between the hospitals (table 3). For urinary tract infections and pneumonia, nearly all treatments involving BSA (28 out of 30) were given to patients with an underlying medical condition. In cases of pneumonia, cystic fibrosis accounted for 17 (71%) of treatments to patients with comorbidities. Prescriptions to patients with an underlying (mostly severe) medical condition, central nervous system (CNS) infection or treatment based on a microbiological sample, accounted for 90% of all doses with BSA (table 4). In the UH, nine admissions of patients with cystic fibrosis accounted for 91 (53%) of total prescriptions with BSA while in the DH, eight admissions of patients with cystic fibrosis were given 19 (20%) of total prescriptions with BSA (p<0.01). When excluding patients with cystic fibrosis, no significant difference in prescription rate of BSA was found between the hospitals.

Blood cultures
In the UH, blood cultures were obtained before or during 77% of all treatments, as opposed to 44% in the DH (p<0.01) (see online supplemental digital content 1, table showing rates for various indications). Out of 14 positive blood cultures, *Staphylococcus aureus* was the most common bacteria (two cases in both hospitals). One case of extended spectrum beta-lactamase (ESBLE) was registered at the UH (see online supplemental digital content 2 for the results and treatments of all infections with positive blood cultures).

Antibiotic doses
Overall, the median dose in mg/kg/day given to children <40 kg was higher in the UH for six out of the seven most commonly prescribed antibiotics given intravenously. A significant difference was found for ampicillin and

cefotaxime (figure 2). For ampicillin, we subgrouped the children above and below 10 kg, and the difference was only significant for children <10 kg (p<0.01) with a median dose of 151 mg/kg/day in the DH and 199 mg/kg/day in the UH. For neonatal infants (<28 days), ampicillin was administered three times a day to nearly all patients in both hospitals (three out of three in the DH, and six out of eight in the UH). For all remaining children <40 kg, ampicillin was mainly administered four times a day in the UH (93%), and three times a day in the DH (54%) (p<0.01). Cefotaxime was also mainly administered four times a day in the UH (8 out of 11, 73%) and three times a day in the DH (8 out of 11, 73%) (p<0.01). The IQR was smaller in the UH for eight of the nine antibiotics. When comparing doses, we controlled for different indications for antibiotic therapy between the hospitals, and only found significant difference in the distribution of indications for ceftriaxone (p=0.02) (see online supplemental digital content 3 for a detailed description of dose comparison).

Seasonal variation
To control for seasonal variation bias in the distribution of indications and choice of antibiotics, we analysed data from the DH corresponding directly with the collection periods at the UH (see online supplemental digital content 4). We revealed no significant differences in adherence rate or BSA use between the hospitals, and the differences in proportions of treatments being pneumonia or upper respiratory tract infections were significant at the same levels as in our main analyses. Also, the number of treatments at the DH was on the same level in the two periods; 65 during the 4 months that we collected data at the UH and 203 during all 12 months.

Table 4 Overview of paediatric prescriptions with broad-spectrum antibiotics (BSA) in a Norwegian university hospital compared with a district hospital

Prescriptions with BSA	Total	University hospital	District hospital	P value*
All BSA, n	269	172	97	
Prescriptions to patients with comorbidities, n (%)	182 (68)	120 (70)†	62 (64)‡	NS
Prescriptions to patients with cystic fibrosis, n (%)	110 (41)	91 (53)	19 (20)	<0.01
Prescriptions to patients with CNS infections, n (%)	40 (15)	19 (11)	21 (22)	0.03
Prescriptions based on microbiological samples, n (%)	130 (48)	111 (65)§	19 (20)¶	<0.01
Prescriptions to patients with comorbidities, CNS infections or based on microbiological samples, n (%)	241 (90)	158 (92)	83 (86)	NS
Second-generation and third-generation cephalosporines, n (% of BSA)	186 (69)	116 (67)	70 (72)	NS
Prescriptions to patients with comorbidities, n (%)	103 (55)	65 (56)	38 (54)	NS
Prescriptions to patients with CNS infections, n (%)	40 (22)	19 (16)	21 (30)	0.02
Prescriptions based on microbiological samples, n (%)	76 (41)	57 (49)	19 (27)	0.03
Carbapenems, n (% of BSA)	34 (13)	24 (14)	10 (10)	NS
Prescriptions to patients with comorbidities, n (%)	31 (91)	24 (100)	7 (70)	NS
Prescriptions based on microbiological samples, n (%)	24 (77)	24 (100)	0 (0)	<0.01
Piperacillin–tazobactam, n (% of BSA)	28 (10)	17 (10)	11 (11)	NS
Prescriptions to patients with comorbidities, n (%)	28 (100)	17 (100)	11 (100)	NS
Prescriptions based on microbiological samples, n (%)	0 (0)	16 (94)	0 (0)	<0.01
Quinolones, n (% of BSA)	7 (3)	1 (0.6)	6 (6)	0.01
Prescriptions to patients with comorbidities, n (%)	7 (100)	1 (100)	6 (100)	N/A
Prescriptions based on microbiological samples, n (%)	1 (14)	1 (100)	0 (0)	N/A
Ceftolozane/tazobactam, n (% of BSA)	14 (5)	14 (8)	0 (0)	0.02
Prescriptions to patients with comorbidities, n (%)	14 (100)	14 (100)	0 (0)	N/A
Doses based on microbiological samples, n (%)	14 (100)	14 (100)	0 (0)	N/A

*χ^2 test. Non-significant results are marked NS. N/A means that the numbers are too small for statistical comparisons.
†Cystic fibrosis (91), chronical kidney disease (9), neurological disease (6), others (14).
‡Cystic fibrosis (19), malignancy (14), inflammatory bowel disease (14), chronical kidney disease (9), neurological disease (5), heart disease (1).
§Blood cultures: extended spectrum beta-lactamase (ESBL) (3), *Klebsiella pneumoniae* (5), bone aspiration: *Kingella kingae* (12), airway sample: *Pseudomonas aeruginosa* (81), *Mycobacterium abscessus* (10).
¶Airway sample: *Pseudomonas aeruginosa* (19).

There was no unusual outbreak of any microorganism during the study periods, but we do not have data about seasonal epidemics of common viruses like influenzae and respiratory syncytial virus (RSV).

DISCUSSION
Principal findings
This study reveals that both hospitals mostly prescribe BSA to patients with severe underlying medical conditions, for CNS infections and/or based on microbiological samples. Adherence to the guideline was high for most indications without significant differences between the hospitals. This indicate that Norwegian paediatricians have a common understanding of main aspects in rational antibiotic use independently of working in a UH or DH.

Limitations and strengths of the study
There are some case-mix differences between the hospitals. Optimally, the general paediatric ward at the UH should also have been included in the comparison as it may have impacted some of our comparisons and inhibited us in performing statistical comparisons of total prescription rates. We have tried to minimise this problem by excluding antibiotics issued as prophylaxis. Information about antibiotic sales to the general ward was also analysed (data not shown), and we conclude that the exclusion of this ward would not have affected our main findings. Furthermore, oncological and cardiological patients are not admitted to the UH, but to another hospital in Oslo. However, only six of the patients who received antibiotics at the DH had a malignancy. Other factors related to different settings, such as bed occupancy
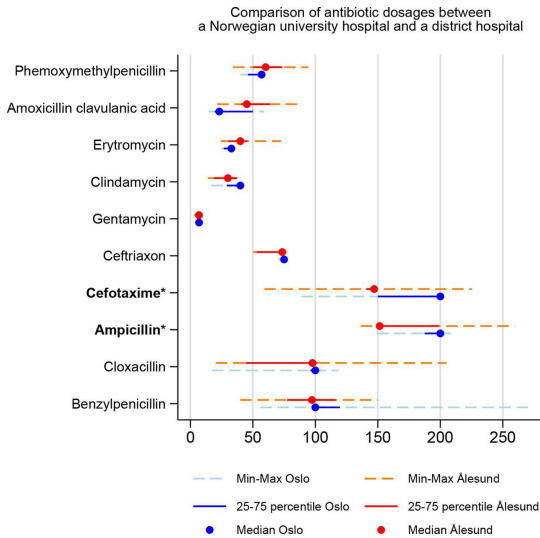
Comparison of antibiotic dosages between a Norwegian university hospital and a district hospital

Figure 2 Comparison of Prescribed Daily Dose (PDD) of common antibiotics in children <40 kg in a Norwegian university hospital and a district hospital. *P-value<0.05, Moods median test.

rate, different composition of population in uptake area and the difference in geographical catchment area between the hospitals, may also have influenced our analyses. When calculating the adherence rate to the guideline, we did not evaluate whether antibiotic therapy was appropriate in first place, the severity of infection or the total duration of treatment; this is, important to be aware of when interpreting our data and are important quality indicators in antibiotic stewardship that should be evaluated in future studies.

Unfortunately, we were not able to organise one entire year of data collection from the UH. Different registration periods could have affected the incidence of infections, prescription rate and the choice of antibiotics, especially for respiratory tract infections. Online supplemental digital content 4 shows that our main conclusions are most certainly not affected by the different registration periods. Minor differences in the numbers for some of the non-respiratory tract infections are more likely to be caused by very small numbers.

A strength of this study is that a long-term period incidence registration limits the chance of temporary casualties like a seasonal epidemic. The inclusion of variables such as comorbidities, microbiological samples and doses further strengthen the results. By conducting the data-collection ourselves, we achieved to collect all necessary data on every single patient and we could process the data based on first-hand knowledge of the registration. This is in opposite to a previous Norwegian point prevalence study were data included less details and were based on a national registry.[11]

Are there clinically relevant differences in antibiotic use between the hospitals?

Children admitted to the UH were prescribed significantly more BSA than in the DH, but this was explained by long-term treatments of patients with cystic fibrosis in the UH. The difference between the hospitals was not significant when comparing BSA use based on the proportion of treatments involving BSA. Our primary aim was to investigate whether use of BSA and adherence rate to antibiotic guidelines differed between the hospitals; we found no reasons to believe that, indicating that the challenges related to these important quality markers in antibiotic stewardship are evaluated with a unified agreement among paediatricians in Norway regardless of working in a UH or DH. A previous study did neither find significant differences in use of BSA between a number of Norwegian anonymous hospitals and increases the generalisability of our results.[11] Nevertheless, more patient-level analyses from other parts of Norway are needed to draw conclusions on prescription practice in other hospitals.

Evaluating our secondary aim, our results revealed several differences between the hospitals. The extensive use of intravenous infusions and combination therapy at the UH can partly be explained by the high number of children with cystic fibrosis receiving long-term combination therapy at the UH. The high use of oral antibiotics at the DH may indicate less severe infections but can also be explained by an early switch from intravenous to oral administration. A systematic review suggests that intravenous to oral switch can occur earlier than previously recommended for many indications.[30]

The distribution of indications varied between the hospitals, mostly due to the significant difference in number of treatments for pneumonia and upper respiratory tract infections. One hypothesis could be that these patients more often were treated as outpatients at the UH. This is supported by a much higher bed occupancy rate and a smaller geographical catchment area for the UH. Finally, the paediatricians at the UH may have regarded more respiratory tract infections as viral. To differ between viral and bacterial aetiology in pneumonia is a main challenge among paediatricians and studies show that most infections are viral.[31 32] The UH have a closer collaboration with the microbiological department and an easier access to an extended panel of swabs and PCR, but analyses for commonly pathogens like *Mycoplasma pneumoniae*, RSV, rhinovirus and influenza viruses are easy and rapidly available in both hospitals.

One could hypothesise that patients treated at the UH in general were more severely ill, reflected by the higher proportion of blood cultures taken. However, this may also be explained by different traditions in the practice and involvement from the microbiological department.

Doses were generally higher at the UH compared with the DH. A European study showed wide variations in antibiotic dosing between different hospitals.[13] According to the guideline,[29] ampicillin and cefotaxime should be given four times a day for children after the neonatal

period, and this represents an area of improvement for the DH. Wider IQR at the DH may indicate that doses were evaluated on a more individual basis rather than standardised. There is a need for studies on antimicrobial dosing in children as recommendations vary between guidelines.[29 33]

Interpretation of the results in relation to the guideline and other studies

Compared with the national point prevalence surveys,[11] use of BSA seems lower in both of our study hospitals, especially when taking into account that prophylaxis was not included. The inclusion of bacterial samples in our study probably explain the high adherence rate to guideline compared with the national survey.[11] Also, compared with international surveys, the children in our study received less BSA and more aminoglycosides.[12 13 16]

For pneumonia, only half of the treatments were in adherence to the guideline in both hospitals, explained by a high use of other narrow-spectrum antibiotics than beta-lactamase susceptible penicillins, especially erytromycin, aminopenicillins and trimethoprim sulfamethoxazole. As vaccines for pneumococcus has been offered to all Norwegian children since 2006, clinicians may think that more pneumonias are caused by other bacteria than pneumococcus. However, a study from 2016 showed that pneumococcus remained the single bacteria accounting for most cases of paediatric pneumonia in Norway.[31] Erytromycin may have been used in cases with PCR positive *Mycoplasma* samples from the nasopharynx. A Cochrane report did, however, not show any clinical benefits of empirical routine coverage for atypical bacteria in pneumonia in adults.[34]

For infections in skin, soft tissue, bone and joint, we were surprised to find extensive use of clindamycin. Even though clindamycin is recommended for severe infections, cloxacillin/dicloxacillin is preferable from an ecological point of view.[35] The short median duration of hospital treatment argues against a high proportion of clinically severe infections. The poor availability of an oral mixture for cloxacillin/dicloxacillin in Norway (not registered by Norwegian authorities) may partly explain the high use of clindamycin which is easily accessible in mixture form. We do not know how many of our patients having penicillin allergy, but both erythromycin and clindamycin are in these cases recommended treatment for their respective indications. However, the prevalence of true penicillin allergy is estimated to be very low, only 0.01%–0.05%,[36] and one study found that among children who reported to have penicillin allergy, only around 20% had true allergy.[37]

Practical implications of the study

The study illuminates the antibiotic consumption in paediatric inpatients in a high-income country with a uniform and stable public healthcare system. The results can be applied in further antibiotic stewardship both in Norway and comparable countries. In Norway, the results should

be evaluated against recommendations in the existing antibiotic guideline in a broader context than just calculating an adherence rate. The study will hopefully also inspire other hospitals to publish individual patient data on antibiotic consumption. Finally, future studies from hospitals should target other important quality indicators such as duration of treatment and whether antibiotics are indicated in first place.

CONCLUSION

Based on this study, we found no reasons to believe that use of BSA and adherence rate to antibiotic guidelines vary significantly between Norwegian UH and DH.

We revealed that ~¾ of the antibiotic treatments were in adherence with the guideline and that use of BSA mostly were related to severe underlying medical conditions, CNS infections and/or microbiological samples. Several issues need further investigation; the large proportional difference between the hospitals in children treated for respiratory tract infections; the high use of other antibiotics than beta-lactam sensitive penicillins in pneumonia, the high use of clindamycin for treatment of infections in skin, soft tissue, bone and joint and the unexplained difference in the doses and dosing frequency of cefotaxime and ampicillin between the hospitals.

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Incidence of blood culture obtained prior to or during antibiotic treatment in hospitalized children in a Norwegian university hospital and a district hospital

Indication	Incidence of at least one blood culture prior to or during antibiotic treatment (%)		p-value, chi square test
	District Hospital	University Hospital	
All treatments	41	77	<0.01
Pneumonia[1]	40	78	<0.01
Urinary tract infection	79	100	0.01
Infection in skin, soft tissue, bone and joint	52	91	<0.01
Sepsis	100	95	NS
CNS infection	43	89	0.03
Upper respiratory tract infection	26	67	0.05
Other infections	29	43	NS

1 Patients with Cystic fibrosis were excluded as these were treated based on airway samples

Positive blood cultures and choice of treatment in hospitalized children in a Norwegian district hospital and a university hospital, 2017

Bacteria in blood culture	District Hospital		University Hospital	
	Numbers	Antibiotic used for treatment	Numbers	Antibiotics used for treatment
Streptococcus Penumoniae	0		2	Benzylpenicillin
Escherichia Coli	1	Ampicillin	2	Ampicillin and Gentamycin Cefotaxime (ESBL)
Staphylococus Aureus	2	Cloxacillin	2	Cloxacillin
Group B Streptococcus	1	Ampicillin	1	Benzylpenicillin
Klebsiella pneumoniae	0		1	Cefotaxime
Granilucatella Elegans	1	Ampicillin and Gentamycin		
Staphylococus Epidermidis- and Hominis[1]	0		1	Cloxacillin
All blood cultures (% of obtained samples)	5 (8)		9 (6)	

1) Probably contamination

Comparison of Prescribed Daily Dose (PDD) of common antibiotics in a Norwegian university hospital and a district hospital. Significant differences in the composition of indications between the two hospitals for any of the comparisons are marked in footnotes. Only patients <40 kg were included.

	District Hospital			University Hospital			
	Number of treatments[1]	Median weight in kg	Median PDD in mg/kg (Interquartile range, min-max)	Number of treatments	Median Weight in kg	Median PDD in mg/kg (Interquartile range, min-max)	P-value[2]
Benzylpenicillin	24	17.1	97 (39, 40-121)	17	15.8	100 (20, 56-273)	NS
Cloxacillin	10	17.8	98 (58, 20-205)	21	11.0	100 (4, 17-119)	NS
Ampicillin	25	11.0	152 (49, 136-259)	37	6.1	200 (13, 149-209)	*<0.01*
Cefotaxime	11	20.0	147 (9, 59-225)	11	13.5	200 (50, 89-200)	*0.030*
Ceftriaxone[3]	11	16.0	74 (22, 50-78)	6	20.0	75 (5, 70-77)	NS
Clindamycin	15	12.0	30 (19, 17-40)	9	16.1	40 (11, 14-40)	NS
Gentamycin	24	11.0	7.0 (1, 3-7)	37	5.9	7.0 (0, 6-7)	NS
Erythromycin	14	16.1	40 (15, 24-72)	4	29.8	33 (8 ,25-35)	NS
Phenoxymethyl-penicillin	50	12.5	60 (23, 36-94)	5	17.0	57 (14, 40-60)	NS

1) Treatments including different daily doses for one drug were regarded as separated treatments for this comparison

2) Moods median test, NS = none significant

3) Significant differences in the composition of indications (p=0.020) (Fishers exact test). District hospital: CNS infection (11), University hospital: CNS infection (2), infection in skin, soft tissue, bone and joint (2), typhoid fever (2)

Pediatric antibiotic prescriptions for different indications in a Norwegian university hospital and a district hospital (June 1th – July 31th and October 17th – December 17th, 2017)

	Total	University hospital	District hospital	P-value[1]
All indications				
Treatments, n	207	142	65	
Health-care acquired infections, n (%)	13 (6)	11 (8)	2 (3)	NS
Treatments involving BSA[2], n (%)	50 (24)	34 (24)	16 (25)	NS
Treatments according to guideline[3,4], n (%)	136 (72)	96 (75)	40 (65)	NS
Pneumonia				
Treatments, n (% of all treatments)	58 (28)	32 (23)	26 (40)	*0.01*
Treatments involving BSA, n (%)	17 (29)	11 (34)	6 (23)	NS
Treatments according to guideline, n (%)	27 (47)	15 (47)	12 (46)	NS
Days of treatment in hospital, median (Interquartile range)	2.0	3.0 (4.0)	2.0 (2.0)	NS
Treatments to patients with comorbidities, n (%)	34 (59)	19 (59)	15 (58)	NS
BSA treatments to patients with comorbidities, n (% of BSA)	17 (100)	11 (100)	6 (100)	NS
Urinary tract infection				
Treatments, n (% of all treatments)	34 (16)	28 (20)	6 (9)	NS
Treatments involving BSA, n (%)	2 (6)	2 (7)	0 (0)	NS
Treatment according to guideline, n (%)	32 (94)	26 (93)	6 (100)	NS
Days of treatment in hospital, median (Interquartile range)	2.0	2.0 (1.5)	1.5 (2.0)	NS
Treatments to patients with comorbidities, n (%)	7 (21)	7 (25)	(0)	NS
BSA treatments to patients with comorbidities, n (% of BSA)	2 (100)	2 (100)	(0)	N/A
Infection in skin, soft tissue, bone and joint				
Treatments, n (% of all treatments)	41 (20)	33 (23)	8 (12)	NS
Treatments involving BSA, n (%)	6 (15)	6 (18)	0 (0)	NS
Treatments according to guideline, n (%)	30 (73)	23 (70)	7 (88)	NS
Days of treatment in hospital, median (Interquartile range)	3.0	3.0 (5.0)	1.5 (4.0)	NS
Treatments to patients with comorbidities, n (%)	4 (10)	1 (3)	3 (38)	*<0.01*
BSA treatments to patients with comorbidities, n (% of BSA)	0 (0)	0 (0)	0 (0)	N/A
Sepsis				
Treatments, n (% of all treatments)	23 (11)	19 (13)	4 (6)	NS
Treatments involving BSA, n (%)	6 (26)	3 (16)	3 (75)	N/A
Treatments according to guideline, n (%)	19 (83)	18 (95)	1 (25)	N/A
Days of treatment in hospital, median (Interquartile range)	3.0	3.0 (3.0)	5.0 (7.0)	NS
Treatments to patients with comorbidities, n (%)	11 (48)	8 (42)	3 (75)	NS
BSA treatments to patients with comorbidities, n (% of BSA)	6 (100)	3 (100)	3 (100)	N/A
Upper respiratory tract infections				
Treatments, n (%)	18 (9)	7 (5)	11 (17)	<0.01
Treatments involving BSA, n (%)	2 (11)	1 (14)	1 (9)	NS
Treatments according to guideline, n (%)	15 (83)	7 (100)	8 (73)	NS
Days of treatment in hospital, median (Interquartile range)	1.0	2.0 (2.0)	1.0 (2.0)	NS
Treatments to patients with comorbidities, n (%)	5 (28)	2 (29)	3 (27)	NS
BSA treatments to patients with comorbidities, n (% of BSA)	1 (50)	1 (100)	0 (0)	N/A
CNS infections				
Treatments, n (%)	16 (8)	9 (6)	7 (11)	NS
Treatment involving BSA, n (%)	13 (81)	7 (78)	6 (86)	NS
Treatments according to guideline, n (%)	13 (81)	7 (78)	6 (86)	NS
Days of treatment in hospital, median (Interquartile range)	1	2.0 (2.0)	1.0 (0.0)	NS
Treatments to patients with comorbidities, n (%)	1 (6)	1 (11)	0 (0)	NS
BSA treatments to patients with comorbidities, n (% of BSA)	1 (8)	1 (14)	0 (0)	N/A
Other infections				
Treatments, n (%)	17 (8)	14 (10)	3 (5)	NS
Treatments with BSA, n (%)	3 (18)	3 (21)	0 (0)	N/A

1. A chi square test was used for proportions and Moods median test for medians. Non-significant results are marked NS. N/A means that the numbers are too small for statistical testing

2. Broad-spectrum antibiotics (BSA) were defined as second- and third generation cephalosporins, carbapenems, piperacillin/tazobactam and ceftolazan/tazobactam

3. The entire treatment is in adherence with the empirical recommendation in The Norwegian guideline [28] and/or in accordance with blood cultures, bone/joint cultures or respiratory tract samples from cystic fibrosis patients (means using any antibiotic (s) that was susceptible by the bacteria, regardless of how the patient was treated initially)

4. Other infections were not included when calculating total compliance with guidelines

Paper II

Can We Optimize Antibiotic Use in Norwegian Neonates? A Prospective Comparison Between a University Hospital and a District Hospital

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Background: Worldwide, a large proportion of neonates are prescribed antibiotics without having infections leading to increased antimicrobial resistance, disturbance of the evolving microbiota, and increasing the risk of various chronical diseases. Comparing practice between different hospitals/settings is important in order to optimize antibiotic stewardship.

Aim: To investigate and compare the potential for improved antibiotic stewardship in neonates in two Norwegian hospitals with different academic culture, with emphasis on antibiotic exposure in unconfirmed infections, treatment length/doses, CRP values and the use of broad-spectrum antibiotics (BSA). All types of infections were investigated, but the main focus was on early-onset sepsis (EOS).

Methods: We conducted a prospective observational cohort study of antibiotic use in a Norwegian university hospital (UH) and a district hospital (DH), 2017. Unconfirmed infections were defined as culture negative infections that neither fulfilled the criteria for clinical infection (clinical symptoms, maximum CRP >30 mg/L, and treatment for at least 5 days).

Results: Ninety-five neonates at the DH and 89 neonates at the UH treated with systemic antibiotics were included in the study. In total, 685 prescriptions (daily doses) of antibiotics were given at the DH and 903 at the UH. Among term and premature infants ($\geq$ 28 weeks), 82% (75% at the UH and 86% at the DH, $p = 0.172$) of the treatments for suspected EOS were for unconfirmed infections, and average treatment length in unconfirmed infections was 3.1 days (both hospitals). Median dose for aminoglycoside was higher for term infants at the UH (5.96, 95% CI 5.02–6.89) compared to the DH (4.98, 95% CI 4.82–5.14; $p < 0.001$). At the UH, all prescriptions with aminoglycosides were gentamicin, while tobramycin accounted for 93% of all prescriptions with aminoglycosides at the DH.

Conclusion: There is a potential for reduction in both antibiotic exposure and treatment length in these two neonatal units, and a systematic risk/observational algorithm of sepsis should be considered in both hospitals. We revealed no major differences between the UH and DH, but doses and choice of aminoglycosides varied significantly.

Keywords: neonatal antibiotic use, antimicrobial resistance, pediatric antibiotic stewardship, antibiotic doses, antibiotic prescriptions

INTRODUCTION

Unnecessary use of antibiotics leads to increased rates of antimicrobial resistance (AMR) and is one of the main challenges in global health (1, 2). AMR rates are low in Norway compared to other countries but has increased during the last decade (3). The Norwegian government has introduced a National Strategy aiming for a 30% reduction in total antibiotic use, and a 30% reduction in the use of broad-spectrum antibiotics (BSA) in hospitals, by year 2020 (4).

Neonates and small children are particularly vulnerable to antibiotic exposure as the diversity of the gut microbiota increases and evolves during the first years of life (5). In addition to increased resistance rates (6, 7), early life antibiotic exposure is associated with the evolvement of various chronic diseases (8–10).

Worldwide, neonates with suspected sepsis are exposed to antibiotics, although only a small proportion have a confirmed infection (11–13). The interpretation of risk factors, clinical symptoms, and biomarkers is challenging, and may explain why antibiotic exposure rates in neonates vary between hospitals, also within the same countries (11, 14). A registry-based population study from Norway (2009–2011) showed that half of term-infants receiving antibiotics were not proven to have a bacterial infection (11). Use of BSA in Norwegian neonates is lower than in older children, but empirical choices of antibiotics vary, and there is a lack of evidence on neonatal dose regimes (15, 16).

Fifteen of the 68 hospitals registered in the database of The Norwegian Institute of Public Health hold a neonatal unit; seven of these units are situated in university hospitals while the rest are situated in smaller district hospitals (all are public hospitals). The university hospitals hold many academic positions and are expected to be in the frontline of developing clinical practice. We therefor speculate whether there are any clearly differences in antibiotic use between centrally located university hospitals and more rural located district hospitals.

The aim of this study was to explore antibiotic use among neonates with and without confirmed infection, with emphasis on choice and dosing of antibiotics, treatment duration, CRP values and the use of BSA. Furthermore, we assessed whether pattern of antibiotic use in neonates differs between university and district hospitals.

Abbreviations: UH, University hospital; DH, District hospital; AMR, Antimicrobial resistance; BSA, Broad-spectrum antibiotics; GA, Gestational age; CNS, Central nervous system.

METHODS

Setting and Design

We designed a prospective observational cohort study, collecting data from 2017 to describe and compare antibiotic use in neonates in a Norwegian university hospital (UH) (Oslo University Hospital, Ullevål) and a district hospital (DH) (Ålesund Hospital).

Hospitals

The study population consisted of all neonates admitted to the neonatal units at the UH and the DH in the study periods. The DH has a neonatal intensive care unit (NICU) consisting of 13 beds and provides regional neonatal service for neonates from gestational age (GA) 26 weeks (after centralization of infants below 26 weeks to a regional UH from February 2017) and offers all kinds of intensive care apart from neonatal surgery and ECMO. The UH has a NICU consisting of 27 beds and provides regional service for neonates with all GA ages and all intensive care needs apart from ECMO and thoracic/heart surgery. Both hospitals mainly treat neonates admitted from the maternity ward, but at the DH critically ill infants (<3 month) can in certain circumstances be referred to the neonatal unit from home.

There are no official national guidelines for antibiotic treatments in neonates in Norway, and most hospitals have local guidelines. In 2017, both study hospitals recommended the use of an aminoglycoside in combination with ampicillin for the treatment of early-onset sepsis. For term infants, the UH recommended aminoglycoside to be dosed 6 mg/kg as one daily administration, while the DH recommended 5 mg/kg. Both hospitals recommended ampicillin to be dosed 50 mg/kg two times a day. None of the hospitals used specific algorithms/observations routines for deciding whether to start antibiotic therapy once neonatal sepsis was suspected. The communication between the laboratory and the neonatal departments is well-established in both hospitals, and both results from CRP analyses and blood cultures are easy and rapidly available for the treating clinicians. In both hospitals, positive blood cultures are alerted directly from the microbiologist in terms of a personal call to the on-duty physician.

Data Collection

At the DH, data were collected from 1st of January—31st of December, 2017. The collection was performed by trained nurses working at the unit and double-checked by the project manager. At the UH, data were collected during 15 weeks in 2017; from 27th of March—20th of May and from 01st of November—31th of December. Data were collected by two MD's working at the unit

and the quality control was performed by the project manager. Educational classes for data collectors were held before the start of the registration.

In both hospitals, patients receiving antibiotics were identified at 08.00 a.m. by the collectors every morning by evaluating all inpatients. In these neonatal wards, outpatient treatment of infections is very uncommon, thus we only included inpatients.

For registrations we modified and extended an international standardized point prevalence protocol developed by the European Center for Disease Prevention and Control (ECDC) (17). The data were stored in an electronical database.

Data collection included the total number of patients in the wards, the total number of patients receiving antibiotics, gender, GA at birth, birthweight, delivery mode, age and weight at the start of antibiotic treatment, type and dose (including intervals) of antibiotics, route of administration, treatment duration (in days), whether it was for treatment of infection or prophylaxis, indication for treatment/prophylaxis, respiratory support (any kind), maximum CRP value and results from blood cultures. For patients receiving antibiotics at the start or end of the registration period we obtained information from previous/remaining days of antibiotic treatment.

The total numbers of live births in the uptake area for both hospitals were collected from the maternity ward and also controlled with the Norwegian birth registry.

Variables and Definitions

Term-infants were defined as GA $\geq$ 37 weeks, premature infants as GA 28–36 weeks and extremely premature infants as GA 23–27 weeks. All prescribed antibiotics were included in our analyses and described in relation to prescriptions, administrations, courses, and admitted patients. One prescription was defined as a daily dose with one antibiotic, an administration was defined as one single dose with one antibiotic, and a course was defined as antibiotic therapy/prophylaxis with one or more antibiotics for a certain indication in a certain continuous time range. Each patient registered at the wards during the daily registration was regarded as one bed day. Doses in mg/kg were based on birthweight until a higher body weight was recorded, and we only compared doses in term infants. Treatment duration was defined as number of days with antibiotic exposure. The total number of live births was used as a denominator for expressing antibiotic exposure within the first 3 days of life. Antibiotics were defined as antibacterials for systemic use (J01). Broad-spectrum antibiotics were defined as second- and third-generation cephalosporins, carbapenems, piperacillin/tazobactam and quinolones, according to the National Strategy against AMR (4).

Surgical prophylaxis was defined as antibiotics given immediately before, during or shortly after surgery to prevent infection. Medical prophylaxis was defined as antibiotics prescribed to prevent infection in patients at risk, but without infectious symptoms and without obtainment of blood culture. Cases where symptoms could be explained by infections, but also by other conditions (for instance prematurity, asphyxia) were not regarded as prophylaxis. Early-onset sepsis (EOS) was defined as suspected sepsis within the first 3 days of life and late-onset sepsis (LOS) when sepsis was suspected after 3 days of

life. Other indications were only used if organ specific symptoms were present (such as skin infections) without suspected sepsis. In theory, all infant with clinical symptoms and exposure for blood culture were classified as sepsis treatments.

Treatments for suspected sepsis were divided in three categories: Culture positive sepsis (which required a positive blood culture and clinical symptoms), culture negative sepsis and no sepsis. The first two categories were regarded as confirmed infections. According to recommendations from the Norwegian Neonatal Network, the diagnosis of a culture negative neonatal sepsis (International Classification of Diseases, 11th revision, P36.9), should only be used if certain criteria are fulfilled; clinical symptoms, CRP >30 mg/L, at least 5 days of antibiotic therapy (or death before 5 days) and whenever other medical conditions are ruled out (18). Thus, we only included neonates with CRP >30 and with at least 5 days of antibiotic treatment (or death before 5 days) when defining culture negative neonatal sepsis. According to the same recommendations, growth of coagulase-negative Staphylococci in blood culture were only considered as neonatal sepsis with CRP >10 and at least 5 days of antibacterial therapy (or death before 5 days). The same method was used to measure CRP in both hospitals: Particle enhanced immune turbidimetry.

Statistics

Statistical analyses were performed using SPSS Statistics 23 (SPSS Inc., Chicago, IL, USA). Comparisons of proportions were done using standard chi-square tests. Means and medians were compared using independent samples t-test and Moods median test, respectively. 95% confidence intervals of means were calculated assuming normal distribution, whereas confidence intervals of medians were calculated using the binomial distribution. Correlation was estimated using Pearson correlation coefficient. P-values <0.05 were considered significant. Because the DH discontinued their service for extremely premature infants with GA < 26 weeks during the study period, antibiotic use in extremely premature infants (GA <28 week) was described without comparisons.

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics (2017/30/REK Midt) and by the Local Data Protection Officials at the two hospitals.

RESULTS

Demographics and Characteristics

In total, 184 patients received 207 courses and 1,588 prescriptions of antibiotics. See **Table 1** for comparisons of demographics and characteristics between the hospitals.

Antibiotic Prescriptions

For term and premature infants, aminoglycosides, and ampicillin accounted for the majority of antibiotic prescriptions, namely 84% at the UH and 85% at the DH (See **Figure 1**). Use of BSA was low (4.3% in total for both hospitals), but the

TABLE 1 | Characteristics of neonates receiving antibiotics in two different Norwegian neonatal units in 2017.

	Total	University Hospital	District Hospital	p-value[a]
ALL				
Patients, n	593	235	358	
Patients exposed to antibiotics, n (%)	184	89 (38)	95 (27)	n/a
Courses with antibiotics, n	208	108	100	
Prescriptions with antibiotics, n	1,588	903	685	
Bed days with antibiotics/total bed days (%, 95% CI)	856/5,486 (16)	492/2,714 (18, 17–19)	364/2,772 (13, 12–14)	n/a
Antibiotic exposure first 3 days/number of live births (%, 95% CI)	150/4,772 (3.1, 2.6–3.6)	73/2,091 (3.5, 2.7–4.3)	77/2,681 (2.9, 2.3–3.5)	n/a
TERM INFANTS				
Patients on antibiotics, n (%)	106 (58)	39 (44)	67 (71)	n/a
Courses with antibiotics, n (%)	108 (52)	40 (37)	68 (69)	n/a
Prescriptions with antibiotics, n (%)	769 (48)	301 (33)	468 (68)	n/a
Prophylaxis/treatments, % of courses	4.6/95.4	7.5/92.5	2.9/97.1	0.278
Male/Female, % of patients	67/33	72/28	64/36	0.401
Cecirian delivery/vaginal delivery, % of patients	25/72	31/62	22/78	0.228
GA (weeks), mean (SD)	39.8 (1.7)	40.1 (2.0)	40.0 (1.6)	0.821
Weigh at start of treatment (g), mean (SD)	3,798 (616)	3,823 (615)	3,774 (616)	0.701
Antibiotic exposure first 3 days/number of live births (%, 95% CI)	92/4,470 (2.1, 1.7–2.5)	36/1,967 (1.8, 1.2–2.4)	56/2,503 (2.2, 1.6–2.8)	0.346
PREMATURE INFANTS				
Patients on antibiotics, n (%)	40 (22)	16 (18)	24 (25)	n/a
Courses with antibiotics, n (%)	42 (20)	17 (16)	25 (25)	n/a
Prescriptions with antibiotics, n	281 (18)	127 (14)	154 (22)	n/a
Prophylaxis/treatments, % of courses	10/90	5.8/94.2	8.0/92.0	0.670
Male/Female, % of patients	58/42	38/62	71/29	0.041
Cecirian delivery/vaginal delivery, % of patients	65/30	50/38	75/25	0.253
GA (weeks), mean (SD)	32.1 (2.4)	31.5 (2.3)	32.7 (2.6)	0.172
Weigh at start of treatment (g), mean (SD)	1,872 (747)	1,481 (537)	2,115 (758)	0.004
Antibiotic exposure first 3 days / number of live births (%, 95% CI)	32/269 (12, 8–16)	13/95 (14, 7–21)	19/174 (11, 6–16)	0.471
EXTREMELY PREMATURE INFANTS[b]				
Patients on antibiotics, n (%)	38 (21)	34 (38)	4 (4)	
Courses with antibiotics, n (%)	58 (28)	51 (47)	7 (7)	
Prescriptions with antibiotics, n (%)	538 (34)	475 (53)	63 (9)	
Antibiotic exposure first 3 days / number of live births (%)	26/33 (79)	24/29 (83)	2/4 (50)	n/a

[a] A chi square test was used for proportions and Student's t-test for means. N/A means that statistic testing was not appropriate because of case mix differences between the hospitals.
[b] The DH only treated infants with GA < 28 weeks between 1th of January and 15th of February.
- GA, Gestational age.
- Term infants (≥ 37 weeks), premature infants (28–36 weeks), extremely premature infants (23–27 weeks).
- Missing data: Delivery mode on three patients (GA>37 weeks) and two patients (GA 28–37 weeks) at the University hospital, weight at one patient (GA >37 weeks) and two patients (28–37 weeks) at the University hospital.

proportion of prescriptions was significantly higher at the DH vs. the UH; 34 prescriptions (5.5%) vs. 11 prescriptions (2.6%), respectively ($p = 0.023$), see **Table 2** for more information. Out of seven BSA courses prescribed at the DH, three were given for LOS, two for lower respiratory tract infection, one for EOS and one for infection in the CNS. Three of these patients received respirator treatment, and three were premature infants. The one course of BSA that was prescribed at the UH were given for EOS to a term infant receiving respirator treatment.

For extremely premature infants, aminoglycosides and ampicillin accounted for 57% of the prescriptions (both hospitals), and BSA use accounted for 15%. For all neonates, 119 (96%) of in total 124 prescriptions with

BSA were second or third generation cephalosporins and 5 (4%) were carbapenems. At the UH, all prescriptions with aminoglycosides were gentamicin, while tobramycin accounted for 93% of all prescriptions with aminoglycosides at the DH.

Startup of Antibiotics

Hundred and twenty-four (83%) out of 150 courses of antibiotics for term and premature infants were started during the first 3 days of life in both hospitals; day one (107, 71%), day two (10, 7%), day three (7, 5%). **Table 2** shows that prescription rate in relation to starting time of the course varied significantly between the hospitals. For extremely premature infants, 29 (50%) out of 58 courses were started within the first 3 days
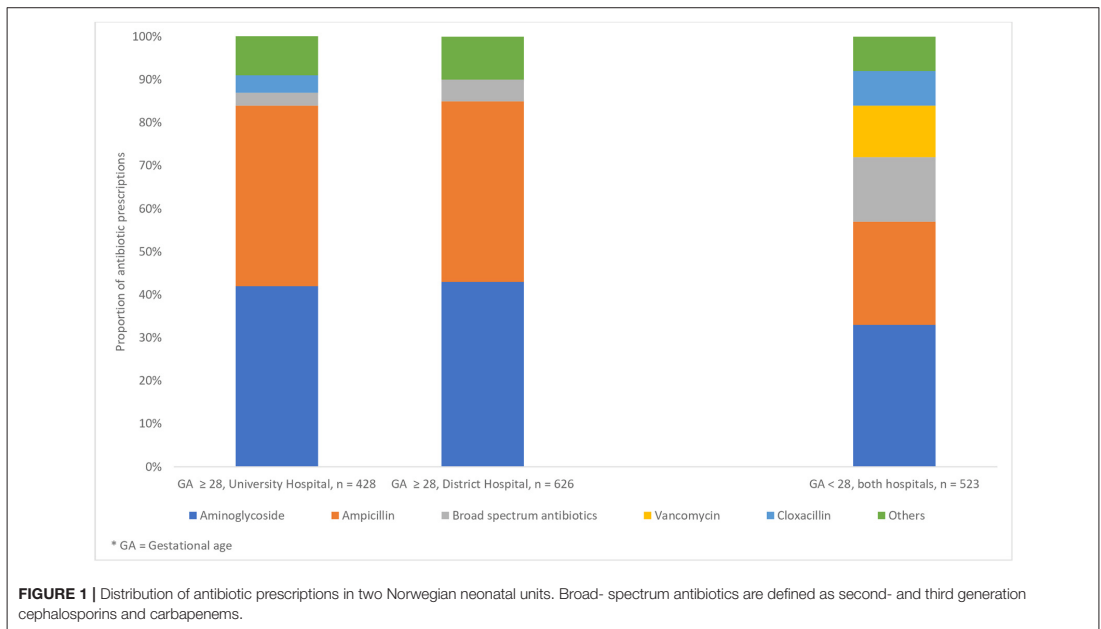
FIGURE 1 | Distribution of antibiotic prescriptions in two Norwegian neonatal units. Broad- spectrum antibiotics are defined as second- and third generation cephalosporins and carbapenems.

of life, 4 (7%) between day three and ten and 25 (43%) after day ten.

Indications for Antibiotic Courses

For term and premature infants, treatment of suspected EOS accounted for 121 (81%) out of 150 antibiotic courses without significant difference between the hospitals (78% at the UH and 84% at the DH, $p = 0.452$). The remaining courses were given for LOS (7%), organ-specific infections without suspected sepsis (7%) and prophylaxis (5%). See **Table 2** for detailed information about the various indications. **Table 3** shows characteristics in treatments of confirmed and unconfirmed EOS among term and premature infants, and highlights that a high number of treatments were given for unconfirmed EOS. Median treatment duration for unconfirmed EOS was 3 days both for term and premature infants and without significant difference between the hospitals (**Table 3**). The maximum CRP value (mean) and the confident intervals increased parallel to the number of treatment days (**Figure 2**). The estimated correlation coefficient was 0.64 ($p < 0.001$). Among extremely premature infants, EOS accounted for 28 (48%) out of 58 antibiotic courses, late-onset sepsis (LOS) for 24 (41%) of the courses and prophylaxis for 6 (10%) of the courses. Mean treatment duration was 4.25 days, 95% CI 3.49–5.01 (EOS + LOS). **Figure 3** shows that a much higher proportion of infants received treatment for confirmed infections among extremely premature infants. See **Supplemental Digital Content 1** for more detailed characteristics of the extremely premature infants. In total, two

patients died during their antibiotic therapy (one at the UH and one at the DH).

Blood Cultures

The rate of blood cultures obtained before initiation of treatments for sepsis (all GA groups) was 99% (171/173). Among term and premature infants, four (two EOS and two LOS) out of 128 (3.1%, 95% CI 0.0–6.2) treatments for suspected sepsis revealed a positive blood culture, corresponding to 0.8/1,000 live born infants. For EOS, the numbers needed to treat for one positive blood culture was 60. Among extremely premature infants, 14 (2 EOS and 12 LOS) out of 52 (27%, 95% CI 13–35) treatments for sepsis included a positive blood culture (12 at the UH and 2 at the DH), corresponding to 14 out of 38 (37%) of extremely premature infants in the units. **Figure 3** clearly illustrates that the proportion of blood culture positive infections was much higher for extremely premature infants.

Overall, the bacteria growing in the cultures were *coagulase negative Staphylococcus* (8), *Streptococcus agalactiae* (5), *Staphylococcus aureus* (3), and *Escherichia coli* (2). Mean treatment duration for infections with *coagulase negative Staphylococcus* was 7.0 days. Five of the treatments involved vancomycin supplemented with one or more of the following antibiotics: aminoglycoside, ampicillin, cloxacillin or ceftazidime. One treatment involved only Cefotaxim and the two last treatments involved an aminoglycoside combined with ampicillin in one case and cloxacillin in the other. Mean treatment duration for infections with *Streptococcus agalactiae* was 9.3 days. Two of the treatments involved mainly

TABLE 2 | Distribution of antibiotic exposure in two Norwegian neonatal units (GA >28) based on start of antibiotic exposure, 2017.

	All	University Hospital	District Hospital	*P*-value[a]
ALL				
Courses, *n*	150	57	93	
Prescriptions, *n*	1,050	428	622	
BSA[b] prescriptions, *n* (%)	45 (4.3)	11 (2.6)	34 (5.5)	*0.023*
Courses including BSA, *n* (%)	8 (5.3)	1 (1.8)	7 (7.5)	0.128
0–3 DAYS				
Courses[c], *n* (%)	124 (83)	49 (86)	75 (81)	0.405
Prescriptions, *n* (%)	861 (82)	369 (86)	492 (79)	*0.003*
BSA prescriptions, *n* (%)	15 (1.7)	11 (3.0)	4 (0.8)	*0.019*
Courses including BSA, *n* (%)	2 (1.6)	1 (2.0)	1 (1.3)	0.761
3–10 DAYS				
Courses[d], *n* (%)	14 (9)	6 (11)	8 (9)	0.695
Prescriptions, *n* (%)	113 (11)	51 (12)	62 (10)	0.317
BSA prescriptions, *n* (%)	10 (9)	0 (0)	10 (16)	*0.002*
Courses including BSA, *n* (%)	2 (14)	0 (0)	2 (25)	0.202
>10 DAYS				
Courses[e], *n* (%)	12 (8.0)	2 (3.5)	10 (11)	0.114
Prescriptions, *n* (%)	76 (7.2)	8 (1.9)	68 (11)	*<0.001*
BSA prescriptions, *n* (%)	20 (26)	0 (0)	20 (29)	0.102
Courses including BSA, *n* (%)	4 (33)	0 (0)	4 (40)	0.294

[a]*Chi square test.*

[b]*BSA: Broad-spectrum antibiotics are defined as second-and third generation cephalosporins and carbapenems.*

[c]*University hospital (UH) treatment: early onset sepsis (48), UH prophylaxis: maternal syphilis (1).*
District hospital (DH) treatment: Early onset sepsis (73), DH prophylaxis: central catheter line (1), vesicourethral reflux (1).

[d]*UH treatment: late onset sepsis (3), eye-infection (1). UH prophylaxis; vesicourethral reflux (2).*
DH treatment: infection in skin, joint and bone (4), late-onset sepsis (3). DH prophylaxis: surgery of transposition of the great vessels (1).

[e]*UH prophylaxis: tracheostomia (1), unknown (1).*
DH treatment: Late onset sepsis (4), lower respiratory tract infection (3), infection in bone, joint and skin (2), CNS infection (1).

benzylpenicillin (partly in combination with an aminoglycoside), two treatments involved an aminoglycoside combined with ampicillin in one case and cloxacillin in the other, and one case involved a combination of vancomycin, ceftazidime, and metronidazole. Mean treatment duration for infections with *Staphylococcus aureus* was 8.3 days. Two of the treatments consisted of cloxacillin monotherapy for more than half of the course and the last case involved an aminoglycoside combined with ampicillin and cloxacillin. For treatment of *Escherichia coli*, one patient was treated with an aminoglycoside combined with ampicillin for 8 days. The other patients, that was treated with an aminoglycoside and ampicillin the first to days and with cefotaxime monotherapy the third day, died during the treatment period. Among the other patients with culture positive sepsis, no fatalities or relapse of infections were registered during the study period.

Doses

Among term infants treated with antibiotics during the first week of life, significantly higher doses of aminoglycosides were used at the UH compared to the DH (**Table 4**). Moreover, the number of daily administrations for ampicillin was higher at the DH.

DISCUSSION

This study reveals that only 1/5 of treatments for suspected EOS in term and premature infants were confirmed infections. Average treatment length for unconfirmed infections was just above 3 days. No significant differences were observed between the hospitals for characteristics of EOS, but doses and choice of aminoglycosides varied between the hospitals.

A strength of this study is the prospective design, that only a few collectors performed the registrations and the small share of missing data. Other studies have excluded coagulase-negative Staphylococci from epidemiological overviews of positive blood cultures because of the probability of contamination (11, 19). Since we included both the treatment length and the CRP values in our data collection, we could apply the definition from the Norwegian Neonatal Network to decide whether or not to regard these as "true" positive cultures (18). An advantage of using an observational cohort design instead of a point-prevalence survey is the lower risk for casualties like ongoing epidemics, to influence the results. Furthermore, our design gives access to variables that requires continuously observational data for the entire treatment period of an antibiotic course. However, a disadvantage with long period registrations is the challenge and feasibility to include more than just a few hospitals.

An important limitation is the low power of the study to detect clinically relevant differences between the hospitals. We aimed to include extremely premature infants also from the DH, but this could not be done due to unexpected hospital centralization for infants with GA < 26 weeks during the study period. Another limitation is the lack of data on maternal risk factors for EOS. We did nor register whether patients were admitted from home, from the maternity ward; as described in methods we could speculate that some patients at the DH were admitted from home reflected by the significantly higher number of term and premature infants >10 days when initiating their antibiotic course. The data collection was performed by clinicians and nurses working at the respective wards, and most clinicians were aware of the study. This may have affected the data in the manner of more prudent antibiotic use than usual. However, as this possible bias was the same in both hospitals it would not affect the comparison between the hospitals. Our sampling did neither report the name of the clinicians prescribing antibiotics.

TABLE 3 | Characteristic in treatment of early-onset sepsis (EOS) in two Norwegian neonatal units, gestational age (GA) ≥ 28 weeks.

	All	University Hospital	District Hospital	*P*-value[a]
All				
EOS treatments, *n*	121	48	73	
Confirmed EOS[b], *n* (%, 95% CI)	21 (17, 10–24)	11 (23, 11–35)	10 (14, 6–22)	
Unconfirmed EOS, *n* (%, 95% CI)	99 (82, 75–89)	36 (75, 63–87)	63 (86, 78–94)	
Unknown (%)	1 (0.8)	1 (2)	0 (0)	0.172
Term infants (GA ≥ 37 weeks)				
EOS treatments, *n* (%)	91 (75)	36 (75)	55 (75)	0.966
Confirmed EOS				
Treatments, *n* (%, 95% CI)	21 (23, 14–32)	11 (31, 16–46)	10 (18, 8–28)	0.173
Treatment duration, mean (95% CI)	5.95 (5.4–6.5)	6.1 (5.3–6.9)	5.8 (5.3–6.3)	0.586
Maximum CRP, mean (95% CI)	61.1 (52.4–69.8)	61.0 (48.4–73.6)	61.3 (49.5–73.1)	0.975
Bloodcultures obtained, *n* (%)	21 (100)	11 (100)	10 (100)	n/a
Positive bloodcultures, *n* (%, 95% CI)	2[c] (10, 0–22)	1 (10, 0–26)	1 (10, 0–29)	0.945
Respiratory support, *n* (%)	5 (24)	4 (36)	1 (10)	0.169
Unconfirmed EOS				
Treatments, *n* (% 95% CI)	70 (77, 68–86)	25 (69, 54–84)	45 (82, 72–92)	0.173
Treatment duration, mean (95% CI)	3.01 (2.7–3.3)	3.2 (2.4–3.9)	3.0 (2.7–3.3)	0.709
Maximum CRP, mean (95% CI)	17.3 (12.9–21.5)	18.2 (12.0–24.5)	16.8 (11.6–22.9)	0.751
Bloodcultures obtained, *n* (%)	69 (99)	24 (96)	45 (100)	0.357
Respiratory support, *n* (%)	28 (40)	11 (44)	17 (38)	0.613
Premature infants (28–36 weeks)				
EOS treatments, *n* (%)	30 (25)	12 (25)	18 (25)	0.966
Confirmed EOS				
Treatments, *n* (%)	0 (0)	0 (0)	0 (0)	n/a
Unconfirmed EOS				
Treatments, *n* (%, 95% CI)	29 (97, 90–100)	11 (92, 76–100)	18 (100, 81–100)	0.221
Treatment duration, mean (95% CI)	3.03 (2.6–3.5)	3.4 (2.5–4.2)	2.8 (2.4–3.3)	0.313
Maximum CRP, mean (95% CI)	8.6 (4.1–13.1)	5.9 (−0.65–12.45)	10.2 (3.42–17.02)	0.305
Bloodculture obtained, *n* (%)	28 (97)	11 (100)	17 (94)	0.434
Respiratory support, *n* (%)	20 (69)	8 (73)	12 (67)	0.737
Unknown				
Treatments, *n* (%)	1 (3.3)	1 (8.3)	0 (0)	0.222

[a]Chi square test was used for proportions and Student's t-test for means. For "all treatments," p-value was based on chi square test for all variables in the section.
[b]Positive blood culture or CRP > 30 and minimum five days of treatment (or death before 5 days). Bloodcultures with Coagulase-negative staphylococci (CoNS) were considered positive if CRP > 10 and minimum 5 days of treatment (or death before 5 days).
[c]One case of Streptococcus agalacticae (GBS) at the University hospital and one case of Staplylococcus epidermidis at the District hospital.

It is reasonable to assume that prescription habits are difficult to change in a manner that would have a significantly impact on our results, but a minor bias can not be excluded. Finally, different registration periods at the two hospitals may have introduced a bias in relation to the seasonality of certain pathogens. One study concluded that there was no seasonal variation in the prevalence of gram-negative microbes causing LOS (20). Another study showed a prevalence of viral infections of 1% at admitted neonates in a neonatal unit (21). Viral infections are known for their seasonality and may have created an imbalance in the two registrations that should be taken into account as they often lead to antibiotic use in infants. However, both hospitals have strict infection control and isolation routines at their neonatal wards, and our main objective of this study was nor to describe the prevalence of infections.

For term and premature infants, use of BSA was low in both hospitals, but the number of prescriptions was higher at the DH. This can partly be explained by four children at the DH receiving BSA after 10 days of age compared to zero at the UH. Also, three of the seven BSA treatments at the DH was for other indications than sepsis and three of the infants were critically ill in term of receiving respirator treatment. One could speculate whether doctors at the UH have a higher threshold for prescribing BSA than in the DH, but taking the low numbers of BSA treatments into account, this difference is probably not clinically relevant. However, this finding should be controlled in future studies.

The difference in the doses of aminoglycosides in term infants is explained by different local guideline recommendations at the hospitals. We did not register any switch of aminoglycoside doses

in term infants during the same course, and one study showed that aminoglycosides safely can be dosed 6 mg/kg every 24 h in term born infants (22). The higher number (mean) of daily administrations with ampicillin at the DH may be explained by the recommendation in a commonly used local Norwegian neonatal supervisor to increase the number of administrations from two up to four per day in severe infections/meningitis (23). From our data, we can not conclude whether there was a difference in severity between the hospitals. More studies focusing on therapeutic drug monitoring of antibiotics in neonates should be conducted in order to optimize dose regimes in the future (24).

The choice of aminoglycoside differed in the UH (gentamicin) and the DH (tobramycin) because of different local guidelines. One study found lower creatinine levels in neonates treated with tobramycin compared to gentamicin, but concluded that the clinical significance of the findings were minimal (25). Tobramycin is the preferred antibiotic to treat infections caused by *Pseudomonas aeruginosa* (26), but this pathogen is rarely detected in the Norwegian infant population (11, 27). As tobramycin is more expensive than gentamicin, the latter can be argued as the aminoglycoside of choice for neonates. By exploring the local hospital guideline at the DH, we could not find any specific reasons (such as local data on microbiological resistance patterns) that would support the use of tobramycin, and from 2018 the DH started to recommend the use of gentamicin as first choice aminoglycoside, partly because of this review of practice.

The rate of antibiotic exposure during the first 3 days of life in term infants is in line with national data from 2009 to 2011 (11), 2.1 and 2.2%, respectively. This indicates no significant change in antibiotic exposure during the last 6 years. However, our rate is low, compared to international literature (28–30). The relation between culture-positive and culture-negative sepsis in our population (1:10) is in the published range (31), while the numbers needed to treat for one positive culture [60] is at the lower side of the literature (11, 32). Our rate of antibiotic exposure for extremely premature infants is in line with data from the USA (33).

We found that 77% of antibiotic courses to term infants for suspected EOS were given to infants without confirmed infections, compared to 54% in the previous national survey (11). In the national survey all antibiotic exposures (including prophylaxis) was included, but only two term infants in our study received prophylactic courses. Also, criteria for culture negative sepsis varied, as the national survey did not include CRP values in the evaluation, and therefore may have overestimated the incidence of confirmed infections. Among premature infants, we observed no confirmed infections in any of the hospitals, indicating a lower threshold for antibiotic therapy. Several studies show that introduction of an algorithm/observational based risk stratification strategy for neonatal sepsis can reduce antibiotic use (30, 34).

Mean treatment duration for unconfirmed EOS (term infants) was shorter than in the national survey from 2009 to 2011, 3 (mean) vs. 4 days (median), respectively. Extremely
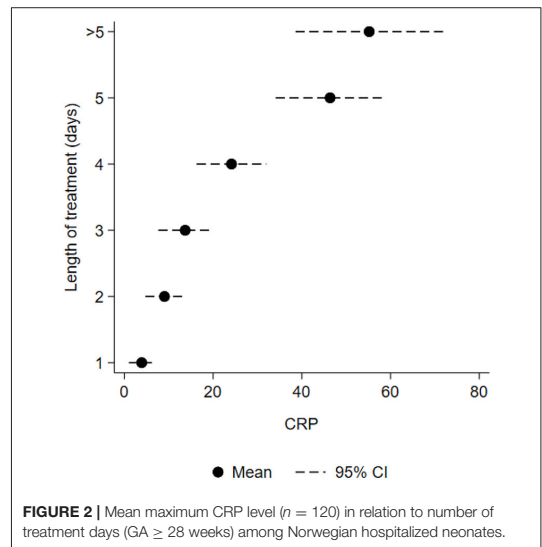
FIGURE 2 | Mean maximum CRP level ($n = 120$) in relation to number of treatment days (GA ≥ 28 weeks) among Norwegian hospitalized neonates.

premature infants in our study were averagely treated 4 days (EOS+LOS). The probability of positive blood cultures beyond 24–48 h is small (35), and studies indicate that treatment safely can be withdrawn after 48 h when clinical suspicion is low (36, 37).

We found that maximum CRP values and 95% CI increased with number of treatment days, indicating that CRP values are regarded as an important factor when deciding treatment length. A recently published study showed that CRP values >30 was uncommon in healthy term infants, supporting the decision of using 30 as cut of level for infection (38). Other biomarkers are also used, but available evidence has not concluded which to prefer (39).

In choice of antibiotics, adherence to local hospital guidelines was high and the use of BSA was low. Previous studies show that several Norwegian hospitals use benzylpenicillin instead of ampicillin in empirical treatments combined with an aminoglycoside (11, 16, 40), and this variation is also present world-wide (41). High prevalence of *Listeria monocytogenes* could justify the use of ampicillin, but according to data from The Norwegian Institute of Public Health, only four cases of listeriosis have been reported among Norwegian children (< 1 year) from 2011 to 2018 (42). Use of ampicillin combined with gentamicin may increase the selection of resistant gram negative bacteria in neonatal units (43). A randomized controlled trial comparing the two regimes found no difference in efficiency or in gut disturbance, but it was underpowered to detect clinical differences (44). Nevertheless, since benzylpenicillin has a narrower antibacterial spectrum probably leading to a lower risk of gut disturbance and resistance, we suggest both study hospitals to consider benzylpenicillin instead of ampicillin in their local guidelines. The commonly used local

FIGURE 3 | Treatments for early-onset sepsis and late-onset sepsis in two Norwegian neonatal units differentiating between confirmed and unconfirmed infections proportionally.
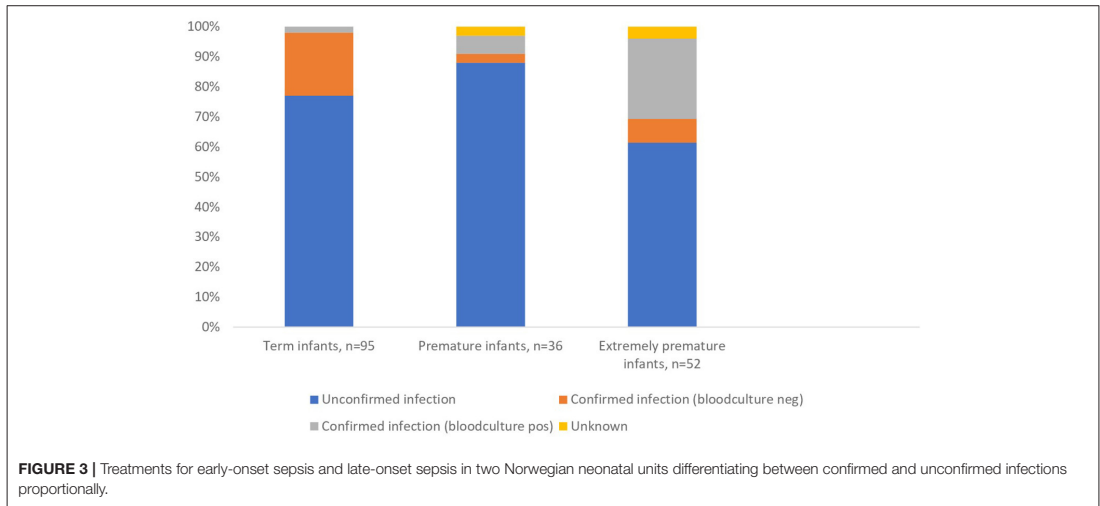
TABLE 4 | Doses of aminoglycosides and ampicillin among term born infants first 10 days of life in two Norwegian neonatal units, 2017.

Antibiotic	University Hospital	District Hospital	P-value[a]
AMINOGLYCOSIDE			
Administrations per day[b] (n), number, mean (95% CI)	39, 0.97 (0,90–1.04)	55, 0.99 (0.97–1.01)	0.912
Dose (mg/kg/day), number, median (95% CI)	39, 5.96 (5.02–6.89)	55, 4.98 (4.82–5.14)	<0.001
AMPICILLIN			
Administrations per day[b,c] (n), number, mean (95% CI)	37, 2.00 (n/a)	55, 2.20 (2.09–2.32)	0.002
Dose (mg/kg/day), number, median (95% CI)	37, 100 (98.48–101.52)	55, 100 (93.89–106.11)	0.248

[a]Student's t test was used for means and Mood median test for medians.
[b]Number of single doses of antibiotics given within 24 h.
[c]DH: Ten daily doses were administered in three daily administrations and one daily dose was administered in four daily administrations (all were 0–3 days old). UH: All daily doses were administered in two daily administrations.
• No switch of daily doses was registered for any of the antibiotics during one single course.

(but national available) Norwegian neonatal supervisor also recommends benzylpenicillin on behalf of ampicillin. At the DH, this change was performed in their local guidelines during 2018.

The definition of medical prophylaxis in neonates is complicated and not well-established. We introduce a definition combining symptoms and the obtainment of blood culture (there is no need for blood culture if the purpose is to prevent an infection) to rule out prophylaxis. Even though we speculate that blood cultures in some cases are taken as part of an implemented routine, our results show a low use of antibiotic prophylaxis in both hospitals compared to international data (41).

The number of extremely premature infants with a positive blood culture (37% of all extremely premature infants in the units, EOS and LOS), is in line with international reports (45, 46). It confirms the need for new strategies to prevent infections in these vulnerable neonates. However, one study identified that one third of extremely premature infants had low risk of EOS and possibly could avoid exposure to antibiotics (47).

Our results can be used in future antibiotic stewardship programs, including research projects, in Norwegian neonatal departments, for instance by introducing interventions/algorithms to reduce antibiotic exposure and treatment duration. A unified national guideline including clear antibiotic recommendations and dose regimes is desirable. For future surveillances, we have suggested a definition of prophylaxis.

CONCLUSION

Based on our study there are no indications of major differences in the pattern of antibiotic use between university and district hospitals in Norway, but term infants at the UH were treated with higher doses of aminoglycosides and fewer daily administrations of ampicillin. Furthermore, gentamicin was the aminoglycoside of choice at the UH, while tobramycin was mainly used at the DH. Even though neonates in Norway receive less antibiotic than in other countries, this study revealed that there is a potential for reduction in both antibiotic exposure and treatment duration for neonates. A systematic

risk/observational stratification of sepsis should be considered in both hospitals.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional Committee for Medical and Health Research Ethics (2017/30/REK Midt). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CT, DB, HB, and BE were involved in the development of the protocol. CT developed the registration form and was responsible for the data collection at Ålesund hospital. AB was responsible for the data collection at Oslo University Hospital, Ullevål. CT and TM did the analyses. CT wrote the first draft. All the authors contributed to the interpretation of the data and revisions of the manuscript and approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped. 2019.00440/full#supplementary-material

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SDC 1) Characteristic in treatment of neonatal sepsis in extremely premature infants (GA < 28), data from two Norwegian hospitals, 2017

Indications	Total
All indications	
Courses, n	58
Treatments for EOS, n (%)	28 (48)
Treatments for LOS, n (%)	24 (41)
Prophylaxis[1], n (%)	6 (10)
Sepsis (EOS and LOS)	
Confirmed sepsis[2,3]	
Treatments, n (% of all sepsis treatments)	18 (35)
Treatment length, mean (95% CI)	7.75 (6.72-8.78)
Maximum CRP, mean (95% CI)	79.8 (60.5-99.1)
Bloodcultures obtained, n (%)	18 (100)
Positive bloodcultures[3], n (%, 95% CI)	14 (78, 52-94)
Unconfirmed sepsis	
Treatments n (% of all sepsis treatments)	32(62)
Treatment length, mean (95% CI)	4.25 (3.49-5.01)
Maximum CRP, mean (95% CI)	5.36 (2.80-7.92)
Bloodcultures obtained, n (%)	32 (100)
Unknown	
Treatments, n (%)	2 (4)

1) Surgical prophylaxis (1), risk for respiratory tract infection (1), unknown (4)

2) Positive blood culture or CRP > 30 and minimum five days of treatment (or death before five days). Bloodcultures with Coagulase-negative staphylococci (CoNS) were considered positive if CRP > 10 and minimum five days of treatment (or death before five days)

3) One case of fatality

4) Coagulase negative Staphylococcus (7), Streptococcus agalacticae (4), Escherichia coli (2), Staphylococcus aureus (1)

• EOS (Early-onset sepsis), LOS (Late-onset sepsis)

Paper III

ORIGINAL ARTICLE

WILEY

Antibiotic use in children before, during and after hospitalisation

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Abstract

Purpose: To investigate ambulatory antibiotic use in children during 1 year before and 1 year after in-hospital antibiotic exposure compared to children from the general population that had not received antibiotics in-hospital.

Methods: Explorative data-linkage cohort study from Norway of children aged 3 months to 17 years. One group had received antibiotics in-Hospital (H+), and one group had not received antibiotics in-hospital (H-). The H+ group was recruited during admission in 2017. Using the Norwegian Population Registry, 10 children from the H- group were matched with one child from the H+ group according to county of residence, age and sex. We used the Norwegian Prescription Database to register antibiotic use 1 year before and 1 year after the month of hospitalisation.

Results: Of 187 children in the H+ group, 83 (44%) received antibiotics before hospitalisation compared to 288/1870 (15%) in the H- group, relative risk (RR) 2.88 (95% confidence interval 2.38–3.49). After hospitalisation, 86 (46%) received antibiotics in the H+ group compared to 311 (17%) in the H- group, RR 2.77 (2.30–3.33). Comorbidity-adjusted RR was 2.30 (1.84–2.86) before and 2.25 (1.81–2.79) after hospitalisation. RR after hospitalisation was 2.55 (1.99–3.26) in children 3 months-2 years, 4.03 (2.84–5.71) in children 3–12 years and 2.07 (1.33–3.20) in children 13–17 years.

Conclusions: Children exposed to antibiotics in-hospital had two to three times higher risk of receiving antibiotics in ambulatory care both before and after

hospitalisation. The link between in-hospital and ambulatory antibiotic exposure should be emphasised in future antibiotic stewardship programs.

KEYWORDS
ambulatory antibiotic use, antibiotic use, antimicrobial resistance, epidemiology, hospital antibiotic use, paediatric antibiotic use

Key points

- In this study we report the association between paediatric antibiotic use in hospital and in ambulatory care.
- Both during the year before and after, children who had received antibiotics in-hospital had almost three times increased risk of antibiotic exposure in ambulatory care compared to the general paediatric population.
- The event of in-hospital antibiotic use did not change antibiotic consumption pattern.
- This study emphasises the advantage of combining antibiotic consumption data from hospitals and ambulatory care when analysing trends in antibiotic use in children.

Plain Language Summary

The novelty of this study is that we have studied antibiotic consumption both in hospital and in ambulatory care in the same patients to better understand the connection between inpatient and outpatient antibiotic use. Also, we included one reference group of children from the general population that were matched according to county of residence, age and sex. We used the national prescription registry to study antibiotic use 1 year before and 1 year after the event of antibiotic exposure in-hospital during 2017. Of those receiving antibiotics in-hospital, 83/187 (44%) were exposed to any antibiotic the year before hospitalisation and 86 (46%) after hospitalisation. The relative risk of receiving antibiotics in ambulatory care compared to the reference group was 2.88 before and 2.77 after hospitalisation. When we adjusted our analyses for underlying medical conditions the relative risk slightly decreased to 2.30 before and 2.25 after hospitalisation. To conclude, ambulatory antibiotic exposure rate did not change after the event of in-hospital antibiotic use, but the risk was two to three times increased compared to the reference group. These findings are relevant when planning future paediatric antibiotic stewardship efforts.

1 | INTRODUCTION

Children exposed to antibiotics have an increased risk of developing resistant bacteria,[1,2] and are in particular risk of long-term adverse effects of antibiotics including various chronic conditions.[3-5] Understanding patterns and risk factors for antibiotic prescriptions in children is essential to optimise antibiotic use. Several reports describing patterns and trends of antibiotic use in children have been published, both from hospitals,[6-12] and ambulatory care.[13-18] However, the possible link between in-hospital and ambulatory antibiotic use is not well studied. Antibiotic stewardship efforts have been requested specifically for groups with recurrent antibiotic use.[19] One study showed that children treated with broad-spectrum antibiotics for pneumonia in ambulatory care had increased risk of hospitalisation compared to children treated with more narrow spectrum antibiotics, even after adjusting for clinical severity measures.[15] Studies have reported that 25%–56% of children receiving antibiotics in-hospital have

comorbidities,[6,9,11] an important aspect when evaluating ambulatory antibiotic use.

Antibiotic exposure in-hospital may represent challenging infections including resistant bacteria and long-lasting infection morbidity.[20] Hospitalisation itself could also cause increased concern from parents lowering the future threshold to seek medical help.[21] On the other side, hospitalisation could lead to more accurate diagnostic work-up and treatments, including follow-up from specialist care. We speculated whether an event of in-hospital antibiotic exposure could predict a change in ambulatory consumption pattern after hospitalisation.

The aim of this study was to examine whether exposure to antibiotics in-hospital was associated with increased use of antibiotics in ambulatory care during 1 year before and during 1 year after hospitalisation, and to investigate whether the risk for antibiotic use in ambulatory care changed after hospitalisation. Furthermore, we aimed to adjust for comorbidities and to investigate risk in different subgroups of children.

2 | METHODS

2.1 | Study design

We conducted an explorative matched data-linkage cohort study of children from 3 months up to 17 years with one group who had been exposed to antibiotics in-hospital (H+) during 2017, and a second group with matched individuals from the general population who had not been exposed to antibiotics in-hospital (H-). Prescriptions in ambulatory care were registered from the Norwegian Prescription Database (NorPD) during 1 year before and 1 year after the month of hospitalisation for the H+ group.[22] An antibiotic prescription was defined as one course of antibiotic dispensed from any Norwegian pharmacy. Ambulatory care prescriptions include all antibiotics given outside an hospital setting, mostly family doctor's offices and outpatient emergency clinics. However, also doctors working in the hospital setting may prescribe ambulatory prescriptions, for instance at discharge from hospital.

2.2 | Children exposed to antibiotics in-hospital (H+)

The children were recruited from the paediatric department in a public district hospital in Ålesund. The number of children living in the hospital catchment area in 2017 was 50 274. All children admitted to the hospital during 2017 who received systemic antibiotics were identified and recruited to the H+ group. The paediatric department consisted of 18 beds and included both medical and surgical patients.

Data were collected every day at 8 AM throughout 2017. Variables registered were sex, age in months, indication for antibiotic use and whether antibiotics were given for treatment or as prophylaxis, type of antibiotic administered, route of administration and comorbidities. The data were registered by study nurses and were double checked by the project manager through the electronic medical record.

Indication for antibiotic use was based on information from the responsible physician in the patient record. Surgical prophylaxis was defined as antibiotics given immediately before, during or shortly after surgery to prevent infection. Medical prophylaxis was defined as antibiotics prescribed to prevent infection in patients at risk. We defined broad-spectrum antibiotics as cephalosporins (except first-generation), carbapenems, quinolones and piperacillin-tazobactam. We subgrouped the children in three age-categories: 3 months to 2 years, 3–12 years and 13–17 years. In cases were children had received antibiotics in-hospital during more than one admission, clinical data from all admissions were registered.

2.3 | Children not exposed to antibiotics in-hospital (H-)

Children in the H- group were identified and selected randomly from the National Population Register. This register includes information of everyone that resides or have resided in Norway. Each child in the H+ group was matched with 10 children in the H- group according to county of residence, month and year of birth, and sex.

2.4 | Comorbidity assessment

For the H+ group, comorbidities were registered at admission to hospital and was based on a predefined list. Common conditions such as allergy, enuresis or asthma without daily medication were not included among the comorbidities. For the H- group, comorbidity status was based on prescriptions of a predefined list of other medicines than antibiotics registered in the NorPD from 2016 to 2018. For commonly used medicines such as inhalation medicines and glucocorticoids at least three prescriptions had to have been dispensed for the individual to be classified with comorbidity. Comorbidities in both groups were classified in five categories: respiratory, neurologic, comorbidities involving immunomodulating medicines, endocrinological and blood/heart/kidney. For the H- group, the conversion from prescription to category was based on clinical judgement by two paediatricians and one pharmacist.

Additionally, to access comorbidity equally between the groups, we also identified all children receiving reimbursable antibiotic prescriptions. In Norway, antibiotics can only be prescribed as an reimbursable prescription if certain criteria related to increased infection risk are present. This alternative comorbidity assessment was used as a supplement to strengthen the evaluation of comorbidity related impact on antimicrobial prescribing.

2.5 | Follow up period in the Norwegian Prescription Database

From 189 eligible children from the hospital registration (H+ group), two were excluded because they were registrated with residency outside the county. Thus, the final cohort consisted of 2057 children, 187 children in the H+ group and 1870 matched controls in the H- group. All children were linked to the NorPD using the national identity number and were followed from 1 January 2016 throughout 31 December 2018. The NorPD is a national prescription database administered by the Norwegian Institute of Public Health.[22] The database contains information on all prescriptions dispensed to individual patients in ambulatory care. We included prescriptions on all systemic antibacterials (ATC group J01). Indication for use was not available. The patients were individually followed from 1 year before the month of hospitalisation to 1 year after the month of hospitalisation. For children with more than one admission, the last admission was used as baseline for the follow-up of ambulatory antibiotic prescriptions.

2.6 | Statistical analysis

Patient demographics were presented using descriptive statistics; categorical variables were presented as numbers and percentages, continuous variables as median with corresponding interquartile range (IQR).

	H+	H-
Total number of children[a]	187	1870
Matched variables[b]		
Sex female	91 (48.7)	910 (48.7)
Age in moths	56 (21–156)	56 (21–156)
0–2 years	71 (38.0)	710 (38.0)
3–12 years	66 (35.3)	660 (35.3)
13–17 years	50 (26.7)	500 (26.7)
Non-matched variables		
Comorbidities[c]	54 (29)	50 (2.7)
Respiratory	13 (7)	19 (1.0)
Neurologic/neuromuscular	25 (13)	6 (0.3)
Involving immunomodulating medicines	11 (6)	5 (0.3)
Endocrinological	1 (1)	9 (0.5)
Blood, heart and kidney	4 (2)	11 (0.6)
H+ specific variables		
Total number of admissions	235	
More than one admission	23 (10)	
All indications	208	
Pneumonia	63 (30)	—
Upper respiratory tract	35 (17)	—
Urinary tract	25 (12)	—
Bone, joint, skin, soft-tissue	18 (9)	—
Central nervous system	14 (7)	—
Sepsis	11 (6)	—
Intra-abdominal	8 (5)	—
Other indications	12 (6)	—
Surgical prophylaxis	13 (6)	—
Medical prophylaxis	9 (4)	—
Treatment length in-hospital	2 (1–5)	—
Treated 0–2 days	102 (55)	—
Treated 3–4 days	38 (20)	—
Treated 5 days or more	47 (25)	—
Children exposed to BSA[d]	39 (21)	—

[a]All variables are presented as number and percentage of total number of children, except age and treatment length in-hospital which are presented as median with corresponding interquartile range.
[b]Ten children in the H− group were matched with one child in the H+ group according to birth month, sex and county of residence.
[c]Comorbidity in the H+ group were registered during hospital admission in 2017. Comorbidity in the H− group was based on prescription history from the Norwegian Presciption Database from 2016 to 2018.
[d]BSA; broad-spectrum antibiotics, defined as all cephalosporins (except first-generation), quinolones, carbapenems and piperazillin-tazobactam.

For children in the H+ group, we analysed antibiotic prescriptions individually during 1 year before hospitalisation and 1 year after hospitalisation. Prescriptions for children in the matched H- group were analysed similarly in the same periods. The main outcomes were numbers and percentages of children exposed to antibiotics in ambulatory care before and after hospitalisation; the secondary outcomes were total number of prescriptions and number of prescriptions per patient in ambulatory care before and after hospitalisation.

To compare one-year antibiotic exposure risk between the H+ group and the H- group at each period (before and after hospitalisation), we calculated relative risk (RR) with 95% confidence interval (CI) using log-binomial regression model and the log-link function. To compare total antibiotic prescriptions, we calculated incidence rate ratio (IRR) with 95% CI using the negative binomial regression model. In both models, we estimated robust SEs to account for correlation due to matching. These analyses were performed for all children overall as well as for selected subgroups. We also estimated RR for different types of antibiotics; penicillin V, amoxicillin, macrolides and certain oral broad-spectrum antibiotics (cotrimoxazole, cefalexin, ciprofloxacin and clindamycin), defined as antibiotics that are not routinely recommended as first-line agents in the guidelines.[23] In all of these analyses, we did additional adjustments for comorbidity. In the analyses including all children, we also adjusted for antibiotic exposure last month before and first month after hospitalisation. We used chi-square test to compare the proportion of ambulatory antibiotic exposure between boys and girls in the H+ group.

For all analyses, we tested for difference in RR and IRR before and after hospitalisation by including a period-by-group interaction term in log-binomial regression models for RR and negative binomial regression models for IRR. To account for repeated measure and intra-individual correlation, we used generalised estimating equation methodology assuming an exchangeable correlation structure. We did these analyses both with and without comorbidity adjustments. A p-value <0.05 was considered significant. All analyses were performed using Stata SE 17.0 (StataCorp LLC, TX) for windows.

3 | RESULTS

Of 50 274 children living in the catchment area, 187 (3.7 per 1000) received systemic antibiotics in-hospital during 2017 and were included in the H+ group. Additionally, 1870 matched children who had not received antibiotics in-hospital were included in the H- group.

Table 1 shows that 29% of the children in the H+ group and 2.7% of the children in the H- group had a comorbidity. Of 23 children in the H+ group receiving antibiotics during more than one admission, 17 (74%) had a comorbidity.

The overall RR for antibiotic exposure in ambulatory care for the H+ group relative to the H- group was 2.88 (95% CI 2.38–3.49) during the year before and 2.77 (2.30–3.33) during the year after hospitalisation (Table 2). After adjusting for both comorbidity and exposures the month before and after hospitalisation, RR was 2.08 (1.60–2.70) before and 2.01 (1.59–2.55) after hospitalisation. Excluding children given in-hospital antibiotics as prophylaxis, RR was 2.99 (2.44–3.65) before and 2.88 (2.39–3.46) after hospitalisation. In the

TABLE 2 Ambulatory care antibiotic exposure in children (3 months to 17 years) during 1 year before and 1 year after the month receiving antibiotics in-hospital. The group of children receiving antibiotic in-hospital (H+) were compared to a group from the general population that had not received antibiotic in-hospital (H−) through the same time-periods

	H+ N (%)	H- N (%)	Relative risk (95% CI)[a]	Comorbidity adjusted relative risk (95% CI)
All children[b]	187	1870		
Antibiotic exposure before	83 (44)	288 (15.4)	2.88 (2.38–3.49)	2.30 (1.84–2.86)
Antibiotic exposure after	86 (46)	311 (16.6)	2.77 (2.30–3.33)	2.25 (1.81–2.79)
Sex				
Sex girl	91	910		
Antibiotic exposure before	45 (50)	141 (15.5)	3.19 (2.47–4.13)	2.46 (1.81–3.34)
Antibiotic exposure after	46 (51)	145 (15.9)	3.17 (2.47–4.08)	2.60 (1.94–3.48)
Sex boy	96	960		
Antibiotic exposure before	38 (40)	147 (15.3)	2.59 (1.94–3.45)	2.14 (1.55–2.94)
Antibiotic exposure after	40 (42)	166 (17.3)	2.41 (1.83–3.17)	1.93 (1.40–2.67)
Age				
0–2 years[c]	71	710		
Antibiotic exposure before	35 (49)	125 (17.6)	2.80 (2.11–3.72)	2.55 (1.86–3.48)
Antibiotic exposure after	40 (56)	157 (22.1)	2.55 (1.99–3.26)	2.31 (1.75–3.07)
3–12 years	66	660		
Antibiotic exposure before	33 (50)	91 (13.8)	3.63 (2.67–4.93)	1.93 (1.21–3.08)
Antibiotic exposure after	29 (44)	72 (10.9)	4.03 (2.84–5.71)	2.48 (1.53–4.00)
13–17 years	50	500		
Antibiotic exposure before	15 (30)	72 (14.4)	2.08 (1.30–3.35)	1.77 (1.09–2.89)
Antibiotic exposure after	17 (34)	82 (16.4)	2.07 (1.33–3.20)	1.69 (1.08–2.65)
Treatment characteristics[d]				
Pneumonia	63	630		
Antibiotic exposure before	36 (57)	113 (17.9)	3.19 (2.42–4.22)	2.40 (1.68–3.43)
Antibiotic exposure after	34 (54)	103 (16.3)	3.30 (2.40–4.53)	2.55 (1.69–3.84)
Upper respiratory tract	35	350		
Antibiotic exposure before	20 (57)	61 (17.4)	3.28 (2.26–4.76)	3.14 (2.19–4.51)
Antibiotic exposure after	19 (54)	65 (18.6)	2.92 (2.15–3.98)	3.18 (2.26–4.47)
Urinary tract infection	25	250		
Antibiotic exposure before	13 (52)	23 (9.2)	5.65 (3.07–10.40)	4.39 (1.60–12.09)
Antibiotic exposure after	17 (68)	47 (18.8)	3.62 (2.59–5.05)	2.94 (1.44–6.02)
Bone, joint, skin, soft-tissue	18	180		
Antibiotic exposure before	8 (44)	18 (10.0)	4.44 (1.78–11.12)	3.19 (1.21–8.38)
Antibiotic exposure after	8 (44)	25 (13.9)	3.20 (1.52–6.73)	2.76 (1.33–5.71)
Treated 5 days or more	47	470		
Antibiotic exposure before	29 (62)	71 (15.1)	4.08 (2.84–5.87)	3.30 (1.91–5.70)
Antibiotic exposure after	29 (62)	85 (18.1)	3.41 (2.55–4.56)	2.74 (1.74–4.33)
More than one admission	23	230		
Antibiotic exposure before	18 (78)	45 (19.6)	4.00 (2.65–6.04)	3.56 (1.97–6.41)
Antibiotic exposure after	18 (78)	40 (17.4)	4.50 (3.08–6.57)	3.57 (1.88–6.80)
Treated with BSA[e]	46	460		
Antibiotic exposure before	18 (39)	55 (12.0)	3.27 (1.96–5.46)	2.06 (1.08–3.95)
Antibiotic exposure after	21 (46)	76 (16.5)	3.17 (2.10–4.80)	2.13 (1.36–3.34)
Comorbidities[e]				
Antibiotic exposure before	40 (74)	13 (26.0)	2.85 (1.64–4.96)	—
Antibiotic exposure after	38 (70)	15 (30.0)	2.35 (1.51–3.65)	—

Abbreviations: 95% CI, 95% confidence interval.
[a]Relative risk was estimated using the log-binomial regression model including estimation for robust *SE*s.
[b]Ten children in the H- group were matched with one child in the H+ group according to birth month, sex and residency.
[c]Ten children were ≤1 year and could not be followed for an entire year prior to hospital admission. Characteristics for in-hospital treatment (H+ group only).
[d]BSA; broad-spectrum antibiotics, defined as cephalosporins (except first-generation), quinolones, carbapenems, and piperazillin-tazobactam.
[e]Not matched according to birth month and sex.

TABLE 3 Ambulatory care antibiotic prescriptions in children (3 months to 17 years) during 1 year before and during 1 year after the month receiving antibiotics in-hospital. Children who had received antibiotics in-hospital (H+) were compared to children from the general population who had not received antibiotics in-hospital (H-) during the same time periods

	H+ N (n/patient)	H- N (n/patient)	Incidence rate ratio (95% CI)[a]	Comorbidity adjusted incidence rate ratio (95% CI)
All children[b]	187	1870		
Antibiotic prescriptions before	288 (1.5)	423 (0.2)	6.81 (4.96–9.34)	3.96 (2.95–5.33)
Antibiotic prescriptions after	339 (1.8)	558 (0.3)	6.08 (4.44–8.31)	4.43 (2.98–6.60)
Sex				
Girls	91	910		
Antibiotic exposure before	181 (2.0)	213 (0.2)	8.50 (5.71–12.64)	4.88 (3.29–7.24)
Antibiotic exposure after	175 (1.9)	288 (0.3)	6.08 (3.86–9.57)	4.49 (2.38–8.47)
Boys	96	960		
Antibiotic exposure before	107 (1.1)	210 (0.2)	5.10 (2.98–8.70)	3.07 (1.96–4.80)
Antibiotic exposure after	164 (1.7)	270 (0.3)	6.07 (3.94–9.37)	4.45 (2.69–7.35)
Age				
0–2 years[c]	71	710		
Antibiotic exposure before	107 (1.5)	174 (0.2)	6.15 (3.59–10.52)	4.28 (2.76–6.63)
Antibiotic exposure after	177 (2.5)	283 (0.4)	6.25 (3.89–10.05)	5.16 (2.92–9.10)
3–12 years	66	660		
Antibiotic exposure before	140 (2.1)	137 (0.2)	10.22 (6.58–15.88)	4.15 (2.48–6.96)
Antibiotic exposure after	113 (1.7)	128 (0.2)	8.83 (5.50–14.17)	3.80 (2.10–6.87)
13–17 years	50	500		
Antibiotic exposure before	41 (0.8)	112 (0.2)	3.67 (1.71–7.85)	2.28 (1.16–4.49)
Antibiotic exposure after	49 (1.0)	147 (0.3)	3.33 (1.64–6.79)	2.20 (1.22–3.97)

Abbreviations: CI, confidence interval.

[a]Incidence rate ratio was estimated using the negative binomial regression model including estimation for robust *SE*.

[b]Ten children in the H- group were matched with one child in the H+ group according to birth month, gender and residency.

[c]Ten children were ≤1 year and could not be followed for an entire year prior to hospital admission.
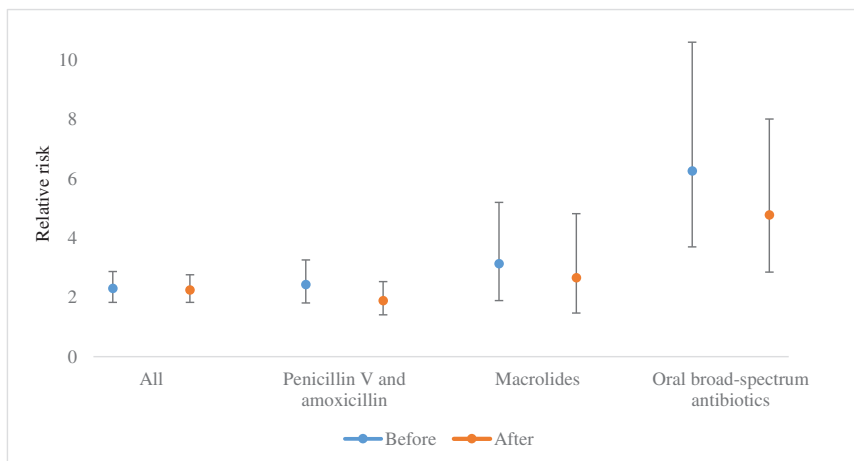
FIGURE 1 Relative comorbidity adjusted risk for different antibiotic exposures in children 1 year before and 1 year after admission to hospital for antibiotic treatment. The reference was a group from the general population that had not received antibiotics in-hospital. Oral broad-spectrum antibiotics are defined as co-trimoxazole, clindamycin, cephalexin and ciprofloxacin. The marked vertical lines indicate the 95% CI [Colour figure can be viewed at wileyonlinelibrary.com]

H+ group, 50% of the girls had been exposed to antibiotics in ambulatory care before hospitalisation versus 40% of the boys ($p = 0.171$). After hospitalisation, 51% of the girls were exposed to antibiotic versus 42% of the boys ($p = 0.219$). Comparing total antibiotic prescriptions, IRR in the H+ group relative to the H- group was 6.81 (4.96–9.34) before and 6.08 (4.44–8.31) after hospitalisation (Table 3).

In the H+ group, 33 (18%) of the 187 children had at least one dispensed reimbursable antimicrobial prescription in the follow-up period, compared to 11 (0.6%) of the 1870 children in the H- group. When adjusting for these cases as an alternative comorbidity assessment, RR for antibiotic exposure was 2.12 (1.66–2.72) before and 2.09 (1.65–2.65) after hospitalisation. IRR for total antibiotic prescriptions was 3.52 (2.56–4.85) before and 2.64 (1.97–3.55) after hospitalisation. We did not reveal relevant differences when comparing the two adjustment methods in any of our analyses (Appendix S1).

In the H+ group, the RR of being prescribed oral broad-spectrum antibiotics was 10.36 (6.32–16.96) before and 7.0 (4.47–10.96) after hospitalisation, while the RR of being prescribed penicillin V or amoxicillin was 3.06 (2.36–3.97) before and 2.08 (1.56–2.76) after hospitalisation. Adjusting for comorbidity, RR decreased for all antibiotic groups (Figure 1).

Counting only one prescription per type of antimicrobial per child, total number of prescriptions in the H+ group was 153 before and 142 after hospitalisation. When merging these to 295 prescriptions, 112 (38%) were penicillin or amoxicillin, 45 (15%) were macrolides, 57 (19%) were oral broad-spectrum antibiotics and 81 (27%) were others.

Of the 57 prescriptions with oral broad-spectrum antibiotics, 38 (67%) were co-trimoxazole, 13 (23%) clindamycin, 10 (18%) cephalexin and eight (14%) ciprofloxacin.

We found no change in RR for antibiotic exposure before and after hospitalisation in the H+ group relative to the H- group for any subgroup of patients. However, RR for penicillin V or amoxicillin exposure decreased after hospitalisation ($p = 0.01$). For an overview of periodical change in RR and IRR, see Appendix S2.

4 | DISCUSSION

To our knowledge, this is the first study examining antibiotic consumption pattern in children before and after receiving antibiotics in-hospital. We found that antibiotic exposure in-hospital was associated with an almost three times increased risk of antibiotic exposure and a more than six times increased incidence rate of total antibiotic prescriptions in ambulatory care both during the year before and the year after hospitalisation. We found no significant change in antibiotic use after the event of in-hospital exposure.

In our study, close to one third of the children in the H+ group had a comorbidity, which is at the lower range of previous reported estimations.[6,9,11] The high incidence rate for total antibiotic prescriptions in ambulatory care for the H+ group is not unexpected given that certain chronical conditions increase the risk of infections and thereby the number of total prescriptions.[24,25] However, also after

adjusting for comorbidities, the IRR remained around four for children up to 12 years. For children 3–12 years, comorbidity adjustment clearly decreased the IRR, probably explained by a high number of children with chronical conditions affecting antibiotic prescribing in this group. Also RR for exposure in the H+ group remained more than doubled in both comorbidity adjustment models. This could have various explanations. These children may have caught an infectious disease with a long-lasting treatment, with high chance of relapse or with multi resistant bacteria. However, most infections have short treatment recommendations,[23] and antibiotic resistance rates are low in Norway.[26] Also, by controlling for reimbursable prescriptions, such cases would probably be included in the adjustment analyses.

Children who received BSA in-hospital had higher risk of re-exposure to antibiotics both before and after hospitalisation compared to the entire H+ group, but after adjusting for comorbidities the risk was on the same level as for the entire H+ group. Moreover, children with prolonged antibiotic treatments in-hospital also had higher risk of re-exposure to antibiotics than the entire H+ group, and this risk remained slightly higher also after adjusting for comorbidities. These observations are not surprising, but important to understand the broad picture in the connection between hospital and ambulatory antibiotic use.

One study in adults showed overuse of antibiotics after hospital discharge,[27] but this was only related to the prescription given at discharge. In our study we notified a slightly trend towards decreased RR and IRR after hospitalisation for the H+ group relative to the H- group for most subgroups. This finding suggests that receiving antibiotics in-hospital does not increase antibiotic consumption after hospitalisation. Children in the H+ group had increased risk of antibiotic use already before admission. We speculate if underlying behavioural and cultural factors among prescribers and parents could be of importance.[28,29] This could include poor reliability of caregivers and language barriers and potentially select a group of children that were both more likely to receive ambulatory antibiotics and to be admitted to hospital. More antibiotic use in ambulatory care initially could also lead to treatment-failure, development of resistant bacteria and a final hospitalisation.[1,2,19]

In the H+ group, the comorbidity adjusted RR for exposure to macrolides and other certain oral broad-spectrum antibiotics was high. This indicate a shift towards antibiotics that are not routinely recommended in empirical guidelines.[23] Even though some of these antibiotics (clindamycin, co-trimoxazole and cephalexin) are acceptable choices according to WHO Access, Watch, reserve (AWaRe) classification,[8] their use should be limited in countries like Norway where more ecological alternatives are preferred given low resistance rates.[26] The high use of co-trimoxazole in the H+ group was surprising as this antibiotic in not recommended empirically, partly due to high resistance rate in *Escherichia coli* and *Streptococcus pneumoniae* isolates.[26] The significant decrease in RR for exposure to penicillin V or amoxicillin in the H+ group after hospitalisation could indicate that threshold for treating respiratory tract infections in ambulatory care was higher after hospitalisation.

In the H+ group, we observed a trend towards more ambulatory antibiotic exposures in girls versus boys both before and after hospitalisation. The finding was somewhat surprising since boys in general tend to have more health problems than girls.[30] A Norwegian registry-based study in children found that boys received more ambulatory antibiotic prescription in the younger age groups, while girls received more ambulatory prescriptions in the older age groups.[13]

A recently published report from the United States recommended antibiotic stewardship programs in all paediatric departments.[31] Most reported stewardship efforts in hospitalised children have been targeted towards antibiotic use during hospitalisation only.[6–11] Hospitalisation could be an opportunity to study antibiotic prescription-history and to tailor an upcoming plan for threshold and choice of antibiotic use, preferably integrated as a mandatory task of a paediatric department. Efficient information flow between hospitals and ambulatory care physicians is also crucial. In Norway, we believe that the expertise and those with greatest motivation for antibiotic stewardship are attached to public hospitals, while many ambulatory care physicians work privately with very busy working schedules. Future studies could desirable also include a reference group of hospitalised children not receiving antibiotics to further understand the impact of antibiotic administration itself.

A strength of this study is that we used prospectively collected clinical data in combination with national registry data. These combinations gave us access to an original matched study of antibiotic consumption pattern before and after hospitalisation. We had no missing data. In Norway, all acute care hospitals are public, facilitating the inclusion of hospitalised children without selection bias, a requirement for conducting a study like this.

One limitation of the study is that comorbidity status in the two groups were obtained by two different methods. Despite this, we regarded this approach most accurate with the purpose to include a wide range of chronical conditions. However, as a control, we also made secondary comorbidity adjustment analyses using identical method in the two groups by approaching reimbursable antibiotic prescriptions as a proxy for infection-related comorbidity. The two different methods of adjustments gave very similar results as shown in Appendix S2, and did not lead to different conclusions. In the subgroup of children 3 months to 2 years, 10 children were 1 year or less and could not be followed for an entire year in the NorPD before admission. However, as we focus on relative differences between the groups, we did not separate these children form our main analyses. Children may have been exposed to antibiotics in-hospital before or after 2017 overlapping with the follow-up period, but in most cases antibiotic courses during hospitalisation are followed by an ambulatory prescription that we could capture through the NorPD. The generalizability of our results could potentially be limited by including only one of 11 counties in Norway. By analysing publicly available statistics from NorPD, we revealed that our county had an antibiotic exposure rate of 16% in 2017 for children 0–19 years, compared to a national rate of 15%.[22] This increases the generalizability of our results, but similar studies from countries with more liberal antibiotic use as baseline would be desirable.

In conclusion, we found that children who had received antibiotics in-hospital had a significantly increased risk of receiving antibiotics in ambulatory care both before and after hospitalisation compared to the general paediatric population. The risk for antibiotic exposure remained more than doubled also after adjusting for comorbidities. We found no major difference in the risk for antibiotic exposure before and after hospitalisation. Future antibiotic stewardship efforts in-hospital should include evaluation of ambulatory antibiotic use in these patients.

ETHICS STATEMENT

This study was approved by the Regional Committee for Medical and Health Research Ethics (2017/30/REK Midt) and by the Local Data Protection Officer at the study hospital. Information letter with the option to withdraw from the study was sent to all participants according to the recommendation from the ethical committee.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Appendix 1a. Comorbidity adjusted risk of ambulatory care antibiotic exposure in children (3 months to 17 years) during one year before and during one year after the month receiving antibiotics in-hospital. Children who had received antibiotics in-hospital (H+) were compared to children from the general population who had not received antibiotics in-hospital (H-).

	Comorbidity adjusted relative risk (95% CI)[1]	Alternative comorbidity adjusted relative risk (95% CI)[2]
All children[c]		
Antibiotic exposure before	2.30 (1.84-2.86)	2.12 (1.66-2.72)
Antibiotic exposure after	2.25 (1.81-2.79)	2.09 (1.65-2.65)
Sex		
Sex girl		
Antibiotic exposure before	2.46 (1.81-3.34)	2.25 (1.59-3.19)
Antibiotic exposure after	2.60 (1.94-3.48)	2.28 (1.62-3.20)
Sex boy		
Antibiotic exposure before	2.14 (1.55-2.94)	2.01 (1.41-2.86)
Antibiotic exposure after	1.93 (1.40-2.67)	1.93 (1.38-2.68)
Age		
0-2 years		
Antibiotic exposure before	2.55 (1.86-3.48)	3.36 (2.60-4.36)
Antibiotic exposure after	2.31 (1.75-3.07)	2.28 (1.72-3.04)
3-12 years		
Antibiotic exposure before	1.93 (1.21-3.08)	2.48 (1.60-3.85)
Antibiotic exposure after	2.48 (1.53-4.00)	2.72 (1.69-4.39)
13-17 years		
Antibiotic exposure before	1.77 (1.09-2.89)	1.34 (0.79-2.27)
Antibiotic exposure after	1.69 (1.08-2.65)	2.33 (1.50-3.62)
Antibiotic type		
Penicillin V and amoxicillin		
Antibiotic exposure before	2.43 (1.81-3.27)	2.39 (1.75-3.25)
Antibiotic exposure after	1.89 (1.37-2.61)	1.69 (1.20-2.39)
Macrolides		
Antibiotic exposure before	3.14 (1.89-5.20)	2.84 (1.68-4.80)
Antibiotic exposure after	2.66 (1.49-4.73)	2.23 (1.20-4.14)
Target antibiotics[d]		
Antibiotic exposure before	6.26 (3.48-11.27)	4.29 (2.22-8.28)
Antibiotic exposure after	4.78 (2.79-8.19)	3.31 (1.80-6.08)

Abbreviations: CI; confidence interval

[a] Comorbidities were based on registration at admission to hospital in the H+ group and on medication history from the Norwegian Prescription Databse in the H- group

[b] Comorbidities were based on reimbursable antibiotic prescriptions in both groups

[c] Relative risk was estimated using the log-binomial regression model including estimation for robust standard errors. Ten children in the H- group were matched with one child in the H+ group according to birth month, gender and residency

[d] Target antibiotics are defined as co-trimoxazole, clindamycin, cephalexin and ciprofloxacin. The marked line indicate the 95 % CI.

Appendix 1b. Comorbidity adjusted incidence rate ratio of ambulatory care antibiotic prescriptions in children (3 months to 17 years) during one year before and during one year after the month receiving antibiotics in-hospital. Children who had received antibiotics in-hospital (H+) were compared to children from the general population who had not received antibiotics in-hospital (H-).

	Comorbidity adjusted incidence rate ratio (95% CI)[a]	Alternative comorbidity adjusted incidence rate ratio (95% CI)[b]
All children[c]		
Anitibiotic prescriptions before	3.96 (2.95-5.33)	3.52 (2.56-4.85)
Antibiotic prescriptions after	4.43 (2.98-6.60)	2.64 (1.97-3.55)
Sex		
Girls		
Antibiotic exposure before	4.88 (3.29-7.24)	4.90 (3.16-7.58)
Antibiotic exposure after	4.49 (2.38-8.47)	2.79 (1.80-4.34)
Boys		
Antibiotic exposure before	3.07 (1.96-4.80)	2.17 (1.52-3.11)
Antibiotic exposure after	4.45 (2.69-7.35)	2.48 (1.69-3.65)
Age		
0-2 years		
Antibiotic exposure before	4.28 (2.76-6.63)	3.54 (2.26-5.55)
Antibiotic exposure after	5.16 (2.92-9.10)	2.86 (1.86-4.40)
3-12 years		
Antibiotic exposure before	4.15 (2.48-6.96)	5.17 (3.01-8.87)
Antibiotic exposure after	3.80 (2.10-6.87)	3.39 (2.11-5.45)
13-17 years		
Antibiotic exposure before	2.28 (1.16-4.49)	1.61 (0.87-2.99)
Antibiotic exposure after	2.20 (1.22-3.97)	1.40 (0.74-2.66)

Abbreviations: CI; confidence interval

[a] Comorbidities were based on registration at admission to hospital in the H+ group and on medication history from the Norwegian Prescription Databse in the H- group

[b] Comorbidities were based on reimbursable antibiotic prescriptions in both groups

[c] Incidence rate ratio was estimated using the negative binomial regression model including estimation for robust standard error. Ten children in the H- group were matched with one child in the H+ group according to birth month, gender and residency

Appendix 2a. Differences in relative risk for ambulatory antibiotic exposure in children one year before and one year after receiving antibiotics in-hospital compared to a group from the general population that did not receive antibiotics in-hospital

	Relative risk		P-value for interaction[a]	Comorbidity adjusted relative risk		P-value for interaction[a]
	Before	After		Before	After	
All children[b]	2.88	2.77	0.719	2.30	2.25	0.775
Girls	3.19	3.17	0.967	2.46	2.60	0.800
Boys	2.59	2.41	0.679	2.14	1.93	0.587
0-2 years	2.80	2.55	0.522	2.55	2.31	0.674
3-12 years	3.63	4.03	0.532	1.93	2.48	0.351
13-17 years	2.08	2.07	0.984	1.77	1.69	0.862
Characteristics in hospital treatments						
Pneumonia	3.19	3.30	0.787	2.40	2.55	0.711
Upper respiratory tract infection	3.28	2.92	0.622	3.14	3.18	0.812
Urinary tract infection	5.65	3.62	0.181	4.39	2.94	0.438
Skin, soft-tissue, bone and joint	4.44	3.20	0.425	3.19	2.76	0.391
Treated five days or more	4.08	3.41	0.327	3.30	2.76	0.482
More than one admission	4.00	4.50	0.622	3.56	3.57	0.824
Treated with broad-spectrum antibiotics[c]	3.27	3.17	0.863	2.06	2.13	0.651
Children with comorbidities	2.85	2.35	0.604	-	-	-

[a] Generalized estimation equation methodology in log-binomial regression models for RR including corrections for within group correlation using the exchangeable correlation structure as well as bootstrap estimation for variance to correct for correlation between the matched clusters.

[b] Children in the two groups were matched according to age, gender and county of residence

[c] All cephalosporines (except first-generation), carbapenems, quinolones and piperacillin-tazobactam

Appendix 2b. Differences in relative risk for exposure to different types of antibiotics in children one year before and one year after receiving antibiotics in-hospital compared to a group from the general population that did not receive antibiotics in-hospital[a]

	Relative risk		P-value for interaction [b]	Comorbidity adjusted relative risk		P-value for interaction[b]
	Before	After		Before	After	
Penicillin G or amoxicillin	3.06	2.08	*0.011*	2.43	1.89	0.169
Macrolides	4.03	3.77	0.834	3.14	2.66	0.652
Oral broad-spectrum antibiotics[c]	10.36	7.00	0.111	6.26	4.78	0.287

[a] Children in the two groups were matched according to age, gender and county of residence

[b] Generalized estimation equation methodology in log-binomial regression models for RR including corrections for within group correlation using the exchangeable correlation structure as well as bootstrap estimation for variance to correct for correlation between the matched clusters.

[c] Co-trimoxazole, ciprofloxacin, clindamycin and cefalexin

Appendix 2c. Differences in incidence rate ratio for total antibiotic prescriptions in children one year before and one year after receiving antibiotics in-hospital compared to a group from the general population that did not receive antibiotics in-hospital

	Incidence rate ratio		P-value for interaction[a]	Comorbidity adjusted incidence rate ratio		P-value comorbidity adjusted[a]
	Before	After		Before	After	
All children[b]	6.81	6.08	0.483	3.96	4.43	0.656
Girls	8.50	6.08	0.173	4.88	4.49	0.781
Boys	5.10	6.07	0.336	3.07	4.45	0.111
0-2 years	6.15	6.25	0.607	4.28	5.16	0.524
3-12 years	10.22	8.83	0.536	4.15	3.80	0.817
13-17 years	3.67	3.33	0.748	2.28	2.20	0.979

[a] Generalized estimation equation methodology in log-binomial regression models for RR including corrections for within group correlation using the exchangeable correlation structure as well as bootstrap estimation for variance to correct for correlation between the matched clusters

[b] Children in the two groups were matched according to age, gender and county of residence

Paper IV

Are infants exposed to antimicrobials during the first 3 months of life at increased risk of recurrent use? An explorative data-linkage study

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Objectives: To investigate whether infants exposed to antimicrobials in hospital during the first 3 months of life had an increased risk of ambulatory antimicrobial use during the following year compared with infants not exposed to antimicrobials during the first 3 months of life.

Methods: Norwegian cohort study of infants less than 3 months consisting of one group exposed to antimicrobials recruited during hospitalization and one group not exposed to antimicrobials. Ten unexposed infants were matched with one exposed infant according to county of residence, birth year and month, and sex. The Norwegian Prescription Database was applied to register antimicrobial use from the month after discharge and 1 year onward. We defined comorbidity based on antimicrobials prescribed as reimbursable prescriptions due to underlying diseases.

Results: Of 95 infants exposed to antimicrobials during the first 3 months of life, 23% had recurrent use compared with 14% use in 950 unexposed infants [relative risk (RR) = 1.7 (95% CI = 1.1–2.5) and comorbidity-adjusted RR = 1.4 (95% CI = 0.9–2.2)]. The recurrence use rate in exposed term infants ($\geq$37 weeks, n = 70) was 27% compared with 12% in their unexposed matches [RR 2.3 = (95% CI = 1.4–3.7) and comorbidity-adjusted RR = 1.9 (95% CI = 1.2–3.2). Of 25 exposed preterm infants, 3 (12%) had recurrent use. The total antimicrobial prescription rate was 674/1000 in the exposed group and 244/1000 in the unexposed group [incidence rate ratio = 2.8 (95% CI = 1.6–4.9)].

Conclusions: Infants exposed to antimicrobials during the first 3 months of life had an increased risk of recurrent use during the following year. This increased risk also appeared in term infants without infection-related comorbidity.

Introduction

Understanding patterns of antimicrobial use is essential to combat increasing antimicrobial resistance.[1,2] Microbiome studies have also reported negative consequences of antimicrobial exposure in early childhood.[3–5] Antimicrobial exposure of the immature microbiome has been linked to increased risk of developing obesity,

asthma, allergy, inflammatory bowel disease, behavioural difficulties and impaired growth.[4,6–12] Recurrent antimicrobial exposures have been shown to be an even stronger risk factor for developing chronic conditions.[6–8]

For infants less than 3 months there is a low threshold for antimicrobial therapy when symptoms of possible infection are present or if the c-reactive protein value is raised. However,

only a small proportion of those treated with antimicrobials have a confirmed infection.[13–15] Thus, risk algorithms and auto-stop antimicrobial functions have been implemented to reduce antimicrobial use.[16,17] After the first few months of life, the risk of severe bacterial infections decreases.[18,19] However, late-infancy studies also indicate that infants receive an excess of antimicrobial prescriptions, mainly for respiratory symptoms.[20,21]

There is a lack of follow-up studies examining subsequent antimicrobial prescriptions in infants. One might suspect that these infants are at risk of recurrent antimicrobial use because of infection-related comorbidities. Also, early-life antimicrobial exposure could lead to antimicrobial resistance or disruption of the microbiome affecting an immature immune system and thereby alter antimicrobial consumption pattern. Finally, behavioural factors like lower threshold for seeking medical help, parental expectations and prescription habits of the doctor could be of importance.[21–23] Thus, we hypothesized that antimicrobial exposure during the first 3 months of life increases the risk of subsequent antimicrobial use.

To explore the hypothesis, we investigated whether infants exposed to antimicrobials in hospital during the first 3 months of life had an increased risk of antimicrobial use in ambulatory care during the following year compared with infants who had not been exposed to antimicrobials during the first 3 months of life. In addition, we aimed to adjust for infection-related comorbidities, to explore if observed associations were different in selected subgroups and to discuss the potential for reduced antimicrobial use.

Methods

Study design

We conducted a cohort study of infants less than 3 months consisting of one group exposed to antimicrobials in hospital (AB+) and one group not exposed to antimicrobials either in hospital or in ambulatory care (AB−).

All infants were followed for 1 year with regards to antimicrobial prescriptions using the Norwegian Prescription Database (NorPD) (Figure 1). We defined the follow-up period as early childhood (varying from 1–12 months to 3–14 months). An antimicrobial prescription was defined as one course of antibiotic dispensed from the pharmacy.

Infants exposed to antimicrobials during the first 3 months of life (AB+)

In Norway, postnatal antimicrobial treatment is given in a public hospital setting. Also, preterm infants or severely sick term infants often remain in hospital care for several weeks.

The infants in this study were recruited from the paediatric department in a district hospital in Ålesund. Infants less than 3 months, born in the county (catchment area) in 2017 and receiving systemic antimicrobials were enrolled in the AB+ group. In the county there were 2681 live births in 2017. The paediatric department consisted of a general paediatric ward with 18 beds and a neonatal intensive care level III unit with 13 beds.

Data were registered by study nurses every day at 8 a.m. throughout 2017 and included gestational age, sex, age in months at the start of antimicrobial therapy, indication for use, type of antimicrobial, respiratory support, complications/other conditions and positive blood cultures. Data were double-checked by the project leader through the electronic medical record.

Indication for treatment was based on symptoms and laboratory or radiological findings. Prophylaxis was defined as antimicrobials given to prevent infections. Respiratory support was defined as invasive ventilation, continuous positive airway pressure (CPAP) or high flow (HF). Complications/other conditions were defined as invasive ventilation, therapeutic hypothermia, thoracic drainage, exchange transfusion, need of immunoglobulin or vasoactive drugs, congenital heart disease, suspected genetic syndrome or severe neurological disease, and any other severe congenital condition requiring surgery or invasive interventions. We defined preterm birth and complications/other conditions as risk factors for recurrent antimicrobial use. Thus, we defined low-risk infants as term infants without complications/other conditions. Preterm birth was defined as gestational age <37 weeks.
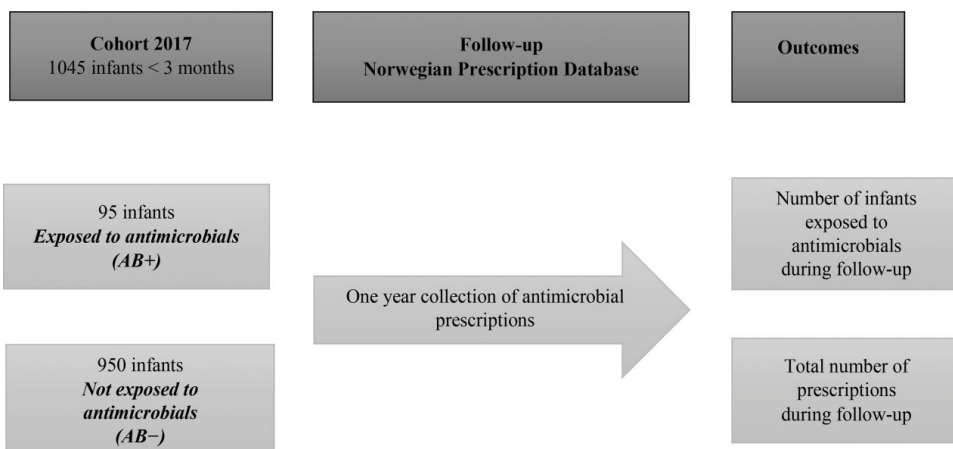

Figure 1. Flow chart of study, including participants, data collection and outcomes.

Infants not exposed to antimicrobials during the first 3 months of life (AB−)

Infants in the AB− group were randomly identified from the National Population Register. This register contains information on everyone who resides in Norway. Each infant in the AB+ group was matched with 10 infants in the AB− group according to county of residence, month and year of birth, and sex. Through the NorPD, we controlled that none of the infants in the AB− group received any antimicrobial prescription during the first 3 months of life.

Follow-up period in the NorPD

Six infants in the AB+ group were excluded: one died during infancy and five were not registered with a home address in the county covered by the hospital. The final cohort consisted of 95 infants in the AB+ group and 950 matched infants in the AB− group. These were linked to the NorPD using the national identity number and were followed from 1 January 2017 throughout December 2018. The NorPD contains information on all prescriptions dispensed to individual patients in ambulatory care in Norway.[24] We included prescriptions of all systemic antibacterials (ATC group J01). Indications for the prescriptions were not available.

To access and adjust for infection-related comorbidity equally between the groups, we identified all infants receiving reimbursable antimicrobial prescriptions due to underlying diseases during the follow-up period. In Norway, the reimbursable antimicrobial prescription system is targeted towards patients with persistent increased infection risk after certain criteria and is actively used by prescribers. Chronic lung conditions, immunodeficiencies and relapsing pyelonephritis would be examples of this. The ICD-10 or ICPC-2 classification systems are used to specify the reason for reimbursement on the prescription. Also, if one expects that the patient would need antimicrobials for at least 3 out of the next 12 months, one can in most cases prescribe a reimbursable prescription.

In Norway, most infants start in day-care centres around the age of 1 year, a relevant aspect when analysing ambulatory prescriptions in infants.

Analyses and outcome variables

Patient demographics were quantified using descriptive statistics and are presented as numbers and percentages. Numbers of treatment days are presented as medians and IQRs.

For infants in the AB+ group, we analysed antimicrobial prescriptions individually from the month after discharge from hospital and 1 year onward. Data for infants in the matched AB− group were analysed for the same period. The main outcome variable was number of infants prescribed antimicrobials in ambulatory care, presented as number and percentage; the secondary outcome variable was total number of prescriptions in ambulatory care, presented as number and prescriptions per 1000 inhabitants. Furthermore, we also present prescriptions of oral broad-spectrum antimicrobials not recommended as first-line agents: macrolides, clindamycin, cefalexin, ciprofloxacin and co-trimoxazole.[25]

To compare the 1 year antimicrobial use rate between the AB+ group and the AB− group, we estimated the relative risk (RR) with 95% CI using a log-binomial regression model and the log-link function. To compare 1 year total antimicrobial prescriptions, we estimated the incidence rate ratio (IRR) with 95% CI using a negative binomial regression model. In both models, we estimated robust standard errors to account for possible correlation due to matching. We also adjusted for infection-related comorbidities. These analyses were performed for all infants and for selected subgroups. Distributions of different antimicrobials are presented as percentages and only one prescription per type of antimicrobial was included per infant for this purpose. Stata SE 17.0 (StataCorp LLC, TX, USA) was used for all analyses.

Table 1. Characteristics of infants less than 3 months exposed to antimicrobials (AB+) compared with infants less than 3 months not exposed to antimicrobials (AB−)

	AB+	AB−
All infants[a]	95	950
Matched variables		
Sex female	32 (33.7)	320 (33.7)
Age 0–1 months	91 (95.8)	910 (95.8)
Age 1–2 months	4 (4.2)	40 (4.2)
Non-matched variables		
Infection-related comorbidities	6 (6.3)	8 (0.8)
Kidney/urinary tract	6 (6.3)	4 (0.4)
Respiratory	0 (0.0)	3 (0.3)
Immunodeficiency	0 (0.0)	1 (0.1)
AB+ specific variables		
Term infants (≥37 weeks)	70 (73.7)	–
Preterm infants (<37 weeks)	25 (26.3)	–
Extremely preterm infants (<28 weeks)	3 (3.2)	–
Admitted to neonatal ICU	89 (93.7)	–
Admitted to general paediatric ward	6 (6.3)	–
Readmissions during first 3 months	0 (0.0)	–
Indication	95	–
Suspected sepsis	78 (82.1)	–
Blood culture proven sepsis	4 (4.2)	–
Skin, soft-tissue, bone, joint	6 (6.3)	–
Pyelonephritis	5 (5.3)	–
Pneumonia	2 (2.1)	–
CNS	1 (1.1)	–
Prophylaxis	2 (2.1)	–
Other	1 (1.1)	–
Invasive ventilation	11 (11.6)	–
Term infants	5 (5.3)	–
Preterm infants	6 (6.3)	–
Any respiratory support[b]	36 (37.9)	–
Term infants	19 (20.0)	–
Preterm infants	17 (17.9)	–
Complications/other conditions[c]	15 (15.8)	–
Total number of antimicrobial days in hospital[d]	671	–
Penicillin V, ampicillin or aminoglycosides	578 (86.1)	–
Carbapenems or third-generation cephalosporins	34 (5.1)	–
Number of days of antimicrobial exposure in hospital	4 (2–5)	–
5 days or more with antimicrobial exposure	26 (27.4)	–

[a]Data are presented as *N* or *n* (%), except number of days of antimicrobial exposure in hospital, which is presented as median (IQR). All percentages (except antimicrobial days) are calculated based on the total number of infants. Data that were not available are marked as '–'.
[b]Invasive ventilation, continuous positive airway pressure (CPAP) or high flow (HF).
[c]Congenital heart failure (3), therapeutic hypothermia (2), thoracic drainage tube (2), exchange transfusion (1), genetic syndrome (1) and ventilator treatment of other causes (6).
[d]One day counted as 1 day for each antimicrobial separately.

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics (2017/30/REK Midt) and by the Local Data Protection Official at the study hospital.

Results

Of 2681 live births in 2017 evaluated for inclusion in this study, 101 (3.8%) children were exposed to antimicrobials in hospital during the first 3 months of life. Ninety-five infants were included in the AB+ group and 950 matched unexposed infants in the AB− group.

Table 1 shows baseline data for both groups. Within the AB+ group, the median number of days of initial antimicrobial exposure was 3 (IQR = 2–5) for low-risk term infants, 4 (IQR = 3–4) for term infants with complications/other conditions and 3 (IQR = 2–4) for preterm infants. Of 26 infants with initial antimicrobial exposure for 5 days or more, 20 were term infants and 6 were preterm infants, and 6 had complications/other conditions.

Table 2 shows that 23% in the AB+ group were prescribed antimicrobials during the follow-up period, while 14% in the AB− group were prescribed antimicrobials during the same period [RR = 1.7 (95% CI = 1.1–2.7) and comorbidity-adjusted RR = 1.4 (95% CI = 0.9–2.2)]. For selected subgroups in the AB+ group, we found the following rates of infants with antimicrobial prescriptions in the follow-up period: infants with complications/other conditions, 3/15 (20%); extremely preterm infants, 1/3

(33%); infants treated for pyelonephritis, 5/5 (100%); and infants needing invasive ventilation, 1/11 (9%). Table 3 shows that the total number of antimicrobial prescriptions was 674/1000 inhabitants in the AB+ group and 244/1000 inhabitants in the AB− group [IRR = 2.8 (95% CI = 1.6–4.9)].

When including only one prescription per type of antimicrobial per infant, nearly half of all prescriptions were penicillin V (Figure 2). The exposure rate for penicillin V was 15/95 (15.8%) in the AB+ group and 81/950 (8.5%) in the AB− group. Of in total 64 prescriptions in the AB+ group, 31 (48%) were trimethoprim, 19 (30%) were penicillin V and 14 (22%) were other antimicrobials. Of 232 prescriptions in the AB− group, 101 (44%) were penicillin V, 36 (16%) were amoxicillin, 27 (12%) were macrolides and 68 (29%) were other antimicrobials. All trimethoprim prescriptions in the AB+ group were reimbursable prescriptions and distributed between six infants, five of whom were treated for pyelonephritis during the first 3 months of life. All prescriptions dispensed were oral formulations.

Discussion

To the best of our knowledge, this is the first follow-up study monitoring recurrent antimicrobial use in infants exposed to antimicrobials in hospital shortly after birth. Interestingly, we found that low-risk term infants had an increased risk of recurrent antimicrobial use (RR = 2.5) compared with infants that had not received

Table 2. Comparison of antimicrobial use in ambulatory care during 1 year in early childhood between infants exposed to antimicrobials during the first 3 months of life (AB+) and infants not exposed to antimicrobials during the first 3 months of life (AB−)

	AB+, N or n (%)	AB−, N or n (%)	RR (95% CI)[a]	Comorbidity-adjusted RR (95% CI)
All infants[b,c]	95	950		
Receiving ambulatory antimicrobials	22 (23.2)	130 (13.7)	1.69 (1.13–2.52)	1.39 (0.86–2.23)
Broad-spectrum antimicrobials[d]	5 (5.3)	39 (4.1)	1.28 (0.52–3.17)	0.68 (0.28–1.67)
All female infants	32	320		
Receiving ambulatory antimicrobials	6 (18.8)	34 (10.6)	1.76 (0.80–3.88)	1.25 (0.48–3.30)
All male infants	63	630		
Receiving ambulatory antimicrobials	16 (25.4)	96 (15.2)	1.67 (1.05–2.64)	1.44 (0.84–2.47)
AB+ specific subgroups[e]				
Term infants (≥37 weeks)	70	700		
Receiving ambulatory antimicrobials	19 (27.1)	83 (11.9)	2.29 (1.41–3.72)	1.94 (1.17–3.23)
Low-risk term infants[f]	62	620		
Receiving ambulatory antimicrobials	17 (27.4)	69 (11.1)	2.46 (1.55–3.91)	2.15 (1.27–3.67)
Preterm infants (<37 weeks)	25	250		
Receiving ambulatory antimicrobials	3 (12.0)	47 (18.8)	0.64 (0.21–1.90)	0.46 (0.12–1.78)
Infants needing any respiratory support	36	360		
Receiving ambulatory antimicrobials	6 (16.7)	57 (15.8)	1.05 (0.49–2.27)	0.78 (0.30–2.02)
Infants treated with antimicrobials for 5 days or more	26	260		
Receiving ambulatory antimicrobials	9 (34.6)	36 (13.8)	2.50 (1.36–4.60)	2.16 (1.08–4.33)

[a]Log-binomial regression model, including estimation for robust standard errors.
[b]The two groups were matched according to county of residence, birth month and year, and gender.
[c]Prescriptions were registered from the month after initial exposure and 1 year onward.
[d]Macrolides, clindamycin, ciprofloxacin, cefalexin and co-trimoxazole.
[e]These variables were only available for the AB+ group.
[f]Infants with predefined complications/conditions were excluded from this group.

Table 3. Comparison of total antimicrobial prescriptions in ambulatory care during 1 year in early childhood between infants exposed to antimicrobials during the first 3 months of life (AB+) and infants not exposed to antimicrobials during the first 3 months of life (AB−)

	AB+, N or n (n/1000)	AB−, N or n (n/1000)	IRR (95% CI)[a]	Comorbidity-adjusted IRR (95% CI)
All infants[b,c]	95	950		
Antimicrobial prescriptions	64 (674)	232 (244)	2.76 (1.55–4.89)	1.43 (0.82–2.51)
Broad-spectrum antimicrobials[d]	6 (63)	55 (58)	1.09 (0.41–2.92)	0.99 (0.32–3.07)
All female infants	32	320		
Antimicrobial prescriptions	18 (563)	59 (184)	3.05 (1.03–9.01)	1.45 (0.41–5.11)
All male infants	63	630		
Antimicrobial prescriptions	46 (730)	173 (275)	2.66 (1.34–5.26)	1.44 (0.79–2.64)
AB+ specific subgroups[e]				
Term infants (≥37 weeks)	70	700		
Antimicrobial prescriptions	54 (771)	144 (206)	3.75 (2.00–7.02)	2.02 (1.09–3.72)
Low-risk term infants[f]	59	590		
Antimicrobial prescriptions	43 (729)	118 (200)	3.64 (1.82–7.30)	2.20 (1.14–4.26)
Preterm infants (<37 weeks)	25	250		
Antimicrobial prescriptions	10 (400)	88 (352)	1.14 (0.28–4.59)	0.56 (0.15–2.13)
Infants needing any respiratory support	36	360		
Antimicrobial prescriptions	19 (528)	98 (272)	1.94 (0.68–5.56)	0.79 (0.30–2.07)
Infants treated with antimicrobials for 5 days or more	26	260		
Antimicrobial prescriptions	27 (1038)	54 (208)	5.00 (1.98–12.62)	2.56 (0.99–6.62)

[a]Negative binomial regression model, including estimation for robust standard errors.
[b]The two groups were matched according to county of residence, birth month and year, and gender.
[c]Prescriptions were registered from the month after initial exposure and 1 year onward.
[d]Macrolides, clindamycin, cefalexin, ciprofloxacin and co-trimoxazole.
[e]These variables were only available for the AB+ group.
[f]Infants with predefined complications/other conditions were excluded from this group.

antimicrobials during the first 3 months of life, even when adjusting for infection-related comorbidity (RR = 2.2).

A previous study from the same hospital found that 27% of hospitalized neonates were exposed to antimicrobials, and that only 14% of treatments for suspected early-onset sepsis were confirmed by blood culture or laboratory criteria (c-reactive protein of 30 mg/L or more).[15] This finding is also in line with other reports.[13,14] Thus, many of the infants in the AB+ group were probably unnecessarily exposed to antimicrobials in the first place. We carefully searched the literature for other studies targeting the risk of recurrent use of antimicrobials in infants, but could not find any comparable studies.

Some studies have argued that single antimicrobial courses in neonates may not be very harmful.[26,27] However, there is increasing evidence of alterations in the developing microbiome,[3–5] increasing the risk of adverse long-term effects.[4,6–12] The results of this study confirmed our hypothesis that children exposed to antimicrobials shortly after birth (AB+) had an increased risk of recurrent use. This is important since recurrent antimicrobial use is reported to be a particular risk factor for adverse long-term effects.[6–8]

We introduced different potential reasons for our hypothesis of increased antimicrobial use in the AB+ group: comorbidities, behavioural factors, disruption of the microbiome and antimicrobial resistance.

Adjustments for infection-related comorbidity slightly decreased the risk of recurrent antimicrobial use in the AB+ group

compared with the AB− group in all comparisons. More specifically, infantile pyelonephritis was the single most identifiable risk factor for recurrent antimicrobial use in the AB+ group. This is not surprising as urinary tract infections often relapse and many receive antimicrobial prophylaxis after the first event of pyelonephritis.[28,29] However, the indication for prophylaxis in this condition has been debated, as the benefit is reported to be small compared with the risk of developing resistance.[28,29]

We found no association between respiratory support in the AB+ group and the risk of antimicrobial prescriptions during follow-up. Furthermore, few preterm infants and infants with neonatal complications/other conditions were prescribed antimicrobials in the follow-up period. Reasons for this could include increased protection from the environment, thereby decreasing the risk of infections. Also, they might have had closer follow-up from specialist care. Given the immature microbiome of premature infants, our results do not support that disruption of the microbiome shortly after birth contributes to more antimicrobial prescriptions in early childhood.[30]

For low-risk term infants in the AB+ group, the risk of recurrent antimicrobial use remained more than doubled, even after comorbidity adjustment. We revealed similar findings when comparing the total number of prescriptions. However, our methods of comorbidity assessment did not necessarily capture all infants with increased infection risk, but previous literature have reported that the majority of infants receiving an antibiotic
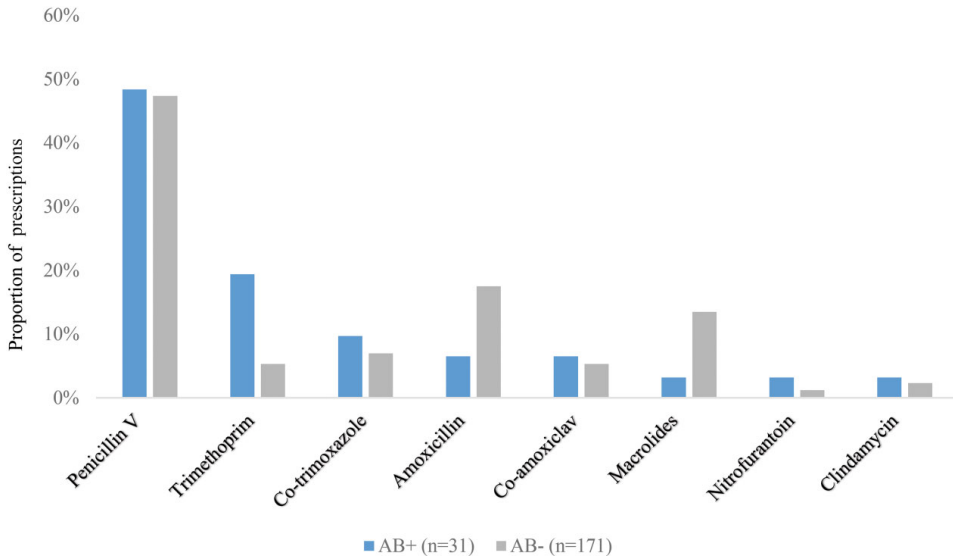
Figure 2. Distribution of ambulatory antimicrobial prescribing pattern for 1 year in early childhood (within the range of 1–14 months of age) in infants exposed to antimicrobials during the first 3 months of life (AB+) and in a control group of infants not exposed to antimicrobials during the first 3 months of life (AB−). Only one prescription per type of antimicrobial included per infant. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

in early life do not have confirmed infections.[13–15] As many infections in early childhood are self-limiting,[21] we speculate whether behavioural factors in parents and prescribers could be of importance. One study from Finland concluded that psychological factors should be considered in infants receiving recurrent antimicrobial prescriptions.[23] Treatments for suspected infection in early life could concern the parents and lead to a lower threshold for seeking a doctor with the expectation of antimicrobial treatment.[21,22] A doctor's prescription attitude may also be influenced by a history of postnatal antimicrobial treatment.[31] More information to outpatient clinics and the public regarding harmful effects of antimicrobial use in early childhood could be helpful. Balanced information regarding a future threshold for antimicrobial use could be implemented as part of neonatal antimicrobial stewardship programmes. The results of our study can encourage future interventions and antimicrobial stewardship programmes to increase focus on the transition between hospitalization and ambulatory care to reduce unnecessary prescriptions.

The high proportion of infants being prescribed penicillin V during the follow-up period reflects that respiratory tract symptoms was a common reason for antimicrobial prescribing.[25] This correlates with a European study reporting that respiratory tract infection was the most common indication for ambulatory antimicrobial therapy in infants.[21] The prescription rate for broad-spectrum antimicrobials, such as macrolides and clindamycin, was low in our study, particularly in the AB+ group. Hence, it is not likely that the AB+ group experienced more episodes of

resistant bacteria. This also corresponds with the low rates of antimicrobial resistance reported in Norwegian children.[18]

Two out of three infants exposed to antimicrobials during the first 3 months of life were males and the proportion of males being prescribed antimicrobials in the follow-up period was also slightly higher than for females in both groups. To compare, a global survey found that 59% of infants receiving antimicrobials in neonatal units were males.[14] A study from Italy reported a 3.5% higher antimicrobial exposure rate for males compared with females in children less than 2 years.[32] Also, studies from Norway confirm this gender gap.[15,24,33] Compared with other countries, the antimicrobial prescription rate during early childhood was in the lower range.[21,32,34]

A strength of our study is that we linked prospectively collected clinical data with the NorPD and the National Population Register, creating a robust cohort of infants for follow-up in the NorPD. It is also a strength that our two groups were matched according to age, gender and residency, to control for these possible confounders, and that we were able to follow prescription activity for the exact same period for the two groups.

One limitation of the study is the lack of variables and potential confounders in the AB− group, namely gestational age, hospitalization and respiratory pressure support. However, by accessing reimbursable prescriptions, we were able to adjust our analysis for infection-related comorbidities. Despite this, our adjusted results may have been subject to confounding by indication due to underlying causes leading to antimicrobial

exposure that could not be captured by the comorbidity assessment used in this study. However, our aim was not to conclude the exact reason for the increased risk in the AB+ group, rather to discuss potential reasons based on our results. For some subgroups, such as preterm infants, we realize that the sample size is low, indicated by the large CIs. Thus, these subgroup analyses should be interpreted with caution and the findings should be validated in future studies using a larger group of preterm infants. Changing residency during the study period could have occurred, affecting the geographical distribution of our patients, but all ambulatory prescriptions would still be recognized through the NorPD. The NorPD captures ambulatory prescriptions only. Thus, infants may have received antibiotics in hospital in the follow-up period. However, antibiotic exposures in hospital would in most cases be followed by an ambulatory prescription at discharge. Also, in the AB+ group we surveyed antibiotic use in hospital during 2017 and we registered no readmissions for antimicrobial use. Finally, we included patients from only 1 out of 11 counties in Norway, possibly limiting the external validity of the study. However, by analysing public statistics from NorPD, we revealed that our county had an antimicrobial exposure rate of 20% in 2017 for children 0–4 years, identical to the national rate.[24] This increases the generalizability of our findings, but similar studies from countries with high rates of antimicrobial use are warranted.

In conclusion, we revealed that infants exposed to antimicrobials during the first 3 months of life had an increased risk of recurrent use during early childhood. Low-risk term infants had a double risk of recurrent antimicrobial use, even after adjusting for infection-related comorbidities. Given the increased vulnerability of infants to antimicrobial exposure, measures should be taken to avoid unnecessary antimicrobial use in infants, as well as after the neonatal period.

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Appendix 1-4

Appendix 1. Definitions

Definitions of terms used in relation to describing antibiotic use

All papers

BSA (broad-spectrum antibiotics): Second to fifth generation cephalosporins, carbapenems, quinolones and piperazillin-tazobactam

Penicillin: Refers to phenoxymethylpenicillin (oral) or benzylpenicillin (intravenous)

Exposure to antibiotics: Any antibiotic given to a patient regardless of quantity

Paper 1-2 (in-hospital descriptions of antibiotic use)

Patient/child/neonate/infant: one patient was defined as one admission

Prescription (in-hospital): one daily dose of one specific antibiotic

Bed-day: Each patient registered at the wards (regardless of receiving antibiotics) during the daily registration counted as one bed-day

Administration: one single dose with one antibiotic

Dose: the quantity of one specific antibiotic given within one day (24 hours) in mg/kg/day

Treatment/course: antibiotic therapy or prophylaxis for a certain indication in a certain continuous time range

Paper 3-4 (in-hospital and ambulatory care descriptions of antibiotic use)

Patient/child/neonate/infant: one patient was defined as one unique patient

Prescription (ambulatory care): One course of antibiotics dispensed at any Norwegian pharmacy

Antimicrobial/antibiotic days (in-hospital): One day counted as one day for each antimicrobial separately

Oral broad-spectrum antibiotics (paper 3): Clindamycin, cephalexin, ciprofloxacin and co-trimoxazole

Oral broad-spectrum antibiotics (paper 4): Macrolides, clindamycin, cephalexin, ciprofloxacin and co-trimoxazole

Age and terminology

Child: 0-18 years (excluding neonates in paper 1 and infants in paper 3)

Neonate: infant admitted to a neonatal intensive care unit

Infant: child less than three months

Term infant: infant with a gestational age of 37 or more

Premature / pre term infant: infant with a gestational age between 28 and 36 weeks

Extremely premature / pre term infant: infant with gestational age bellow 28 weeks

*Children are in some general phrases used to describe all children/infants/neonates, but this should be easy to understand

*In paper 3 and 4 premature infants refer to all infants with gestational age bellow 37 weeks

*Children 0-18 years refers to up to the day of turning 18 years.

Other definitions

Early-onset sepsis (EOS): suspected sepsis the first three days of life

Late-onset sepsis (LOS): suspected sepsis after the first three days of life

Appendix 2. Registration forms (in Norwegian)

Registrering av antibiotika bruk til barneavdelingen

Presiseringer:

- hvis en pasient får flere systemiske antibiotika (for en eller flere indikasjoner), skal hvert medikament registreres for seg (én linje per antibiotikum)
- hvis en pasient får flere systemiske antibiotika for samme indikasjon, registreres indikasjonen flere ganger

Registrert av: _____

Dato: _____

Avdelingsnavn: _____

Antall pasienter kl. 08:00: _____

Antall pasienter som får antibiotika: _____

Person-nummer	Bosatt i fylket?	Fornavn	Kjønn	Alder	Vekt	Antibiotikum	Dose	Målenhet	Adm per døgn	Adm. måte	Klassifisering	Indikasjon	Komorbiditet	BK tatt?	Mikrobiologi

Variabel	Kommentar
Alder	I måneder
Antibiotikum	f.eks. Ampicillin, tobramycin
Dose og måleenhet	Gram (g), milligram (mg), tablett* (tbl, benyttes kun for kombinasjonspreparater)
Admin.måte	Oralt (O), intramuskulært (IM), intravenøst (IV) (OBS inhalasjonsantibiotika, dråper og salver skal ikke registreres)
Klassifisering	Samfunnservervet infeksjon (Samf), helsetjenesteassosiert infeksjon (HAI), kirurgisk profylakse: (Kirpro),medisinsk profylakse (Medpro) eller ukjent.
Indikasjon	Infeksjonstypen behandlingen er rettet mot, eller profylaksen skal forebygge, eller ukjent, se indikasjonsliste i mal.
Komorbiditet	Se komorbiditetsliste. Hvis bruk av immunsupprimerende legemidler, merk JA
Mikrobiologi	Navn på bakterie, resistensbestemmelse sjekkes i etterkant. Følgende inkluderes: Blod, spinalvæske, pleuravæske, bein, leddvæske, luftveissekret hos barn med CF

Registrering av antibiotika bruk til nyfødtavdelingen

Presiseringer:

- hvis en pasient får flere systemiske antibiotika (for en eller flere indikasjoner), skal hvert medikament registreres for seg (én linje per antibiotikum)
- hvis en pasient får flere systemiske antibiotika for samme indikasjon, registreres indikasjonen flere ganger

Registrert av: _____

Dato: _____

Avdelingsnavn: _____

Antall pasienter kl. 08:00: _____

Antall pasienter som får antibiotika: _____

Hjelpe-nummer	Etternavn Mor	Etternavn Far	Bosatt i fylke?	Kjønn	GA	Forl. metode	Alder	FV	Vekt	Navn antibiotikum	Dose	Mål enhet	Ant adm per døgn	Adm. måte	Klassifisering	Indikasjon	Komplikasjoner/andre tilstander	Resp. støtte	CRP	Blod Kultur tatt	Svar blodkultur

Variabel	Kommentar
GA	Gestasjonsalder
Alder	I dager
FV	Fødselsvekt
Vekt	Dagens vekt (registreres de dagene det taes vekt)
Navn på antibiotikum	f.eks Ampicillin
Dose og måleenhet	Gram (g), milligram (mg), tablett* (tbl, benyttes kun for kombinasjonspreparater)
Admin.måte	Oralt (O), intramuskulært (IM), intravenøst (IV), ved inhalasjon (Inhal) eller rektalt (R)
Klassifisering	Inf (=infeksjon) Pro (=profylakse) Hvis blodkultur er tatt registreres Inf
Indikasjon	Infeksjonstypen behandlingen er rettet mot, eller profylaksen skal forebygge, eller ukjent, se indikasjonsliste i mal. Ikke ved profylakse.
Komplikasjoner/andre tilstander	Se egen liste
Respirasjonsstøtte	Respirator, BiPAP, CPAP eller HF.
Blodkultur	Skriv JA/NEI og marker hvis det var tatt etter oppstart med antibiotika. Skriv navn på evt bakterie.

Appendix 3. Comorbidity assessment

Assessment through hospital-registrations

Comorbidity list in children (paper 1 and 3)

Pulmonary and allergic disease:

-Asthma were only registered if using daily inhalation medication

-Common allergy was not classified as a comorbidity, only if the patient was on systemic steroids at admission

Heart diseases

-Only if surgery performed within last 3 years or planned within one year OR follow-up by paediatric cardiologist required at least once a year OR if the patient used daily medicine for the heart condition

Nevrological and neuromuscular disease

-including, but not limited to genetic syndroms, epilepsy and cerebral palsy

-If diagnostic work up was not ready, but the patient had a clear delay in motoric, language or social functioning, need of daily medication etc, they were classified with a comorbidity

Gastrointestinal disease

-including, but not limited to intestinal bowel disease (IBD), celiacic disease, severe gastritis

-Mild gastrointestinal reflux, including sporadic treatments with proton pump inhibitors in the infant period, were not classified as comorbidity

-Patients being examined for unspecific abdominal pain were not classified as comorbidity

Oncological and/or haematological disease

-Active cancer treatment or treatment finalized within last 3 years

-Benign haematological diseases were classified as comorbidity if requiring follow up in specialist care at least every year, or if using daily medication for the condition at

time of admission, or if needing blood transfusion at least two times the last year before admission

Endocrinological disease:

-Included, but not limited to diabetes, thyroid disorders, disorders related to the adrenal gland or patients receiving any hormonal treatment.

-Patients followed for failure to thrive or abcent of puberty was not classified as comorbidity in cases were a clearly diagnosis was abcent

Immunodeficiencies

-Registered if followed at specialist care for recurrent infections or fever episodes even if a clearly diagnosis was not set.

Immunomodulating medicines

-All patients receiving systemic immunomodulating medicines at time of admission were registered; systemic steroids were also included, but at least three month of therapy was required for being classified as immunomodulating medicine.

Kidney/urology

-Vesiculourethral reflux was classified as comorbidity if being graded as at least 2.

-Patients requiring follow up for a kidney related diagnosis at specialist care at least once a year was classified with a comorbidity independent of the above

-Isolated enuresis was not classified as comorbidity

Skin

-Severe skin conditions with the need of daily immunomodulating medication (systemic or topical) for the last three months were included

Surgery

-Surgery performed within the last three months expecting to result in long-term comorbidity were included

Not included

-Isolated conditions related to psychiatry, eyes, hearing and orthopaedics were not included if not any of the above mentioned criteria were fulfilled

Comorbidity (neonatal complications / other conditions) in infants

-Used as assessment for sub-group analyses in paper 4

The following were registrated

-Receiving invasive ventilation

-Receiving therapeutic hypothermia

-Receiving thoracic drainage (chest tube)

-Receiving blood exchange transfusion

-Receiving immunoglobulin or vasoactive drugs

-Congenital heart disease (except minor insignificant findings on echocardiography)

-Suspected genetic syndrome, metabolic disease or severe neurologic disease

-Any other congenital condition requiring surgery or invasive interventions

-For those admitted to the paediatric ward, the definitions for children were used.

Assessment through the Norwegian Prescription Database

Reimbursable antibiotic prescriptions

-Used as main proxy for comorbidity assessment in paper 4, and as additional
assessment in paper 3.
-Any reimbursable systemic antibiotic prescription prescribed in each study-
participant`s individually follow-up period. The ICD-10 or ICPC-2 diagnostic code
noted on the prescription was used for sorting different types of comorbidities.

Other medical prescriptions

-Used as main proxy for comorbidity assessment in paper 3 for children not exposed to
antibiotics in-hospital

Prescriptions of the following ATC groups were included as proxies for comorbidities:

-A02: drugs for acid related disorders

-A03F: propulsives

-A10: drugs in diabetes

-B01A: antithrombotic agents

-B02BD: blood coagulation products

-C: cardiovascular system

-D07: dermal corticosteroids

-H: hormones for systemic use, excl. sex hormones and insulin

-L01: antineoplastic agents

-L03: immunostimulants

-L04: immunosuppressants

-N03: antiepileptics

-R03AC: selective beta-2-adrenoreceptor agonists, inhalants

-R03AK: adrenergics in combination with corticosteroids or other drugs, inhalants

-R03BA: glucocorticoids, inhalants.

For the following groups of commonly used medicines in children, a minimum of three prescriptions had to have been dispensed for the individual to be classified with comorbidity: R03AC, R03AK, R03BA (inhalation medicines), D07 (dermal corticosteroids), A02 (acid related disorders), A03F (propulsives) and H02AB (glucocorticoids for systemic use). Prescriptions with H01BA02 (desmopressin) was excluded because enuresis was not regarded a comorbidity.

The conversion from prescription to comorbidity-category was based on clinical judgement by two pediatricians and one pharmacist. The categories of comorbidities were: respiratory, neurologic, comorbidities involving immunomodulating medicines, endocrinological and blood/heart/kidney. This was done both for comorbidities deriving from the hospital registration and those deriving from prescriptions in the NorPD.
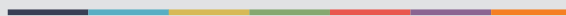
Appendix 4. Admission and bed-day statistics from Ålesund hospital (in Norwegian)

Antall episoder											
			2010	2011	2012	2013	2014	2015	2016	2017
Klinikk for barn og unge	AL Barne- og ungdomsavdelinga	AL Barnemed. post	918	863	768	758	765	961	934	931
Klinikk for kirurgi Ålesund	AL Kirurgisk avd.	AL Kir. barnepost		77	130	213	192	234	228	232
Klinikk for kirurgi Ålesund	AL Ortopedisk avd.	AL Ort. barnepost		116	202	170	138	150	146	129
Klinikk for kirurgi Ålesund	AL ØNH avd.	AL ØNH barnepost		173	253	232	224	213	193	151
Klinikk for kirurgi Ålesund	AL Tann/kjeve avd.	AL Tann/kjeve barnepost		5	7	4	4	4	6	2
Klinikk for kirurgi Ålesund	AL Øyeavdelingen	AL Øye barnepost		11	9	1	5	5	4	11
Sum innlagte med + kir			918	1245	1369	1378	1328	1567	1511	1456
Klinikk for barn og unge	AL Neonatal avd.	AL Neonatal post	401	423	396	408	387	310	310	358

Liggedøgn										
		2010	2011	2012	2013	2014	2015	2016	2017
Klinikk for barn og unge	AL Barnemed. post	2074	2364	1942	1893	1831	2245	2267	2011
Klinikk for kirurgi Ålesund	AL Kir. barnepost		113	248	345	323	371	348	417
Klinikk for kirurgi Ålesund	AL Ort. barnepost		333	493	555	331	306	307	224
Klinikk for kirurgi Ålesund	AL Tann/kjeve barnepost		21	26	5	17	10	12	4
Klinikk for kirurgi Ålesund	AL ØNH barnepost		222	314	254	266	285	229	180
Klinikk for kirurgi Ålesund	AL Øye barnepost		12	9	6	14	15	10	27
Sum liggedøgn med + kir		2074	3065	3032	3058	2782	3232	3173	2863
Klinikk for barn og unge	AL Neonatal post	3159	3759	3632	2850	3061	3177	2417	2772

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