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ORIGINAL ARTICLE

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 sub grouped 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).

TABLE 1 Demographic overview of one group of children (3 months to 17 years) receiving antibiotics in-hospital during 2017 (H+) and one group of children from the general population not receiving antibiotics in-hospital during 2017 (H-)

	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 *SE*s 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 (co-trimoxazole, 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.

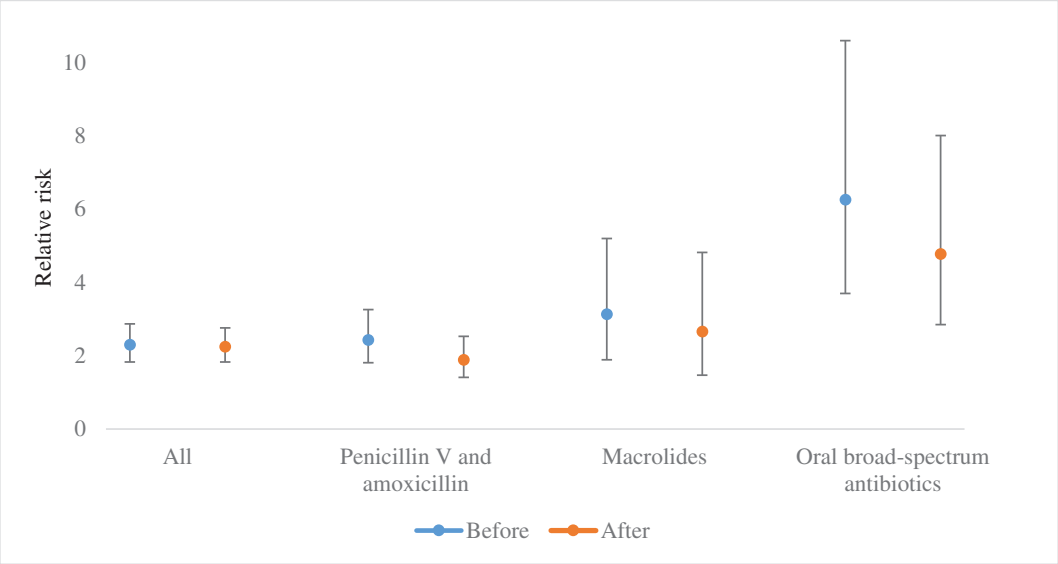

FIGURE 1 Relative comorbidity adjusted risk for different antibiotic exposures in children 1 year before and 1 year after admission to hospital for antibiotic treatment. The reference was a group from the general population that had not received antibiotics in-hospital. Oral broad-spectrum antibiotics are defined as co-trimoxazole, clindamycin, cephalexin and ciprofloxacin. The marked vertical lines indicate the 95% CI

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.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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.

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