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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.
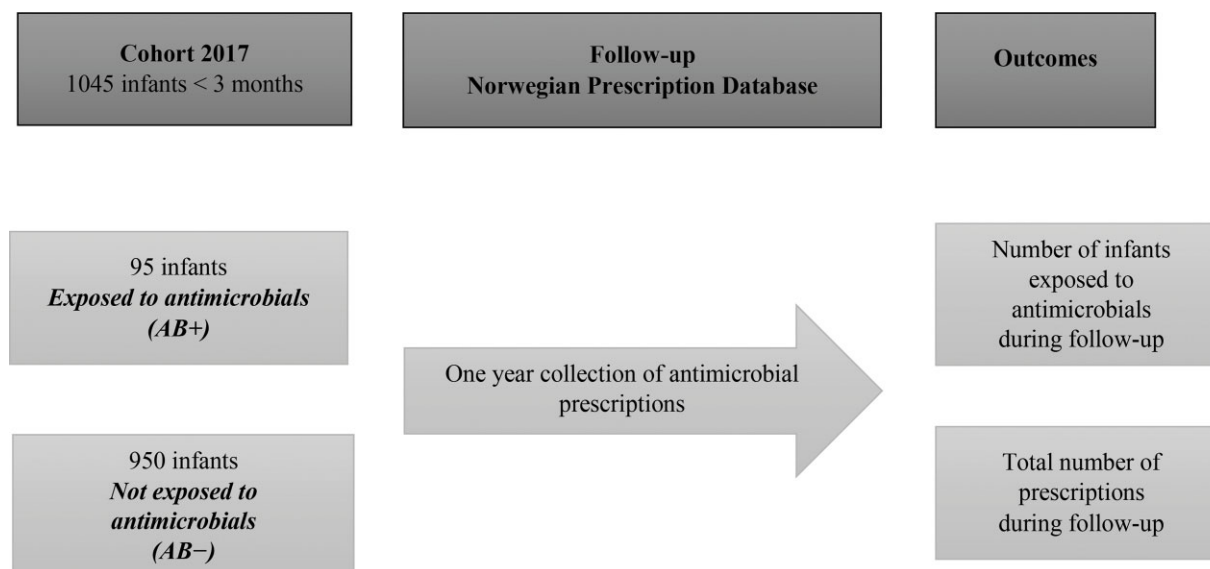

Figure 1. Flow chart of study, including participants, data collection and outcomes.

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
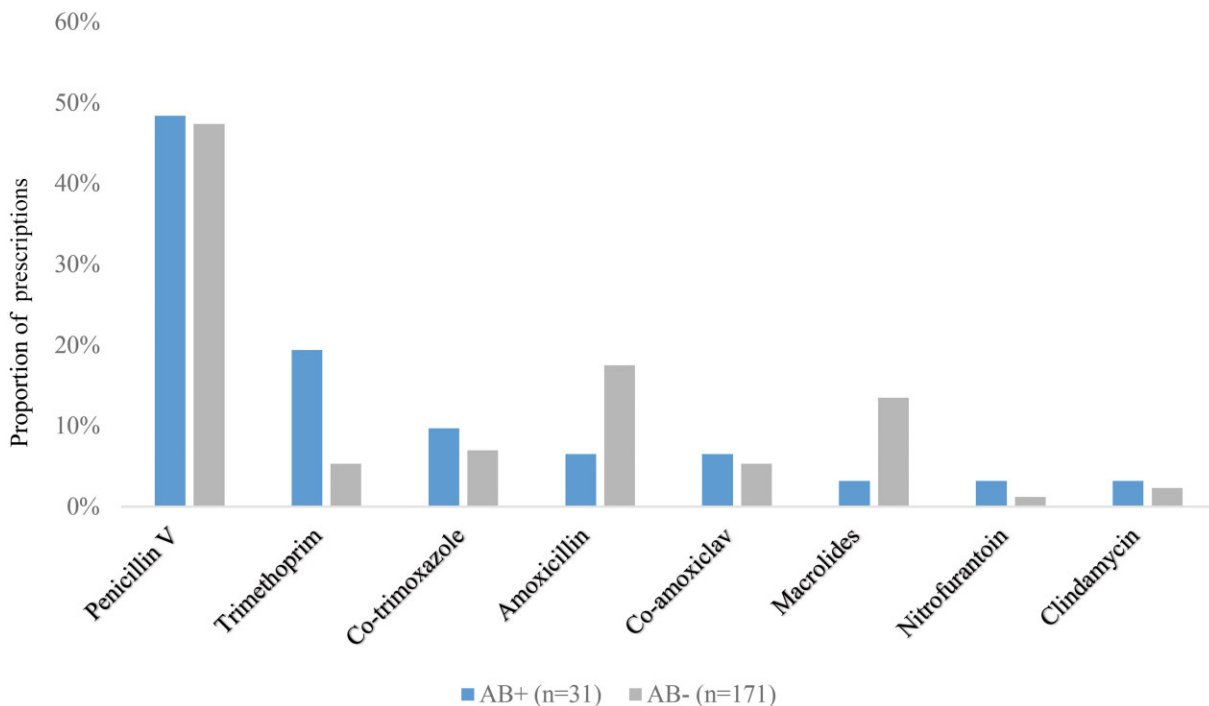
Figure 2. Distribution of ambulatory antimicrobial prescribing pattern for 1 year in early childhood (within the range of 1–14 months of age) in infants exposed to antimicrobials during the first 3 months of life (AB+) and in a control group of infants not exposed to antimicrobials during the first 3 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.

Transparency declarations

None to declare.

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