Antibacterial use by birth year and birth season in children 0-2 years in Norway

Sanna Beckstrøm[a,b*], Kristian Svendsen[a] and Lars Småbrekke[a]

[a]*Department of pharmacy, Faculty of Health Sciences, UiT the Arctic University of Norway*

[b]*Vitusapotek Byåsen Butikksenter, Trondheim*

Correspondence: Sanna Beckstrøm, Email sannabeck@gmail.com Telephone +47 916 15 451

ORCIDs: SB: 0000-0002-9240-6168. KS: 0000-0003-3481-3539. LS: 0000-0001-6475-3368

ABSTRACT

Introduction: Consumption of antibacterials in children follows seasonal cycles, and time to first treatment depends on birth season. The aim of this study was to describe dispensing rate, one-year periodic prevalence, and age at first prescription in children aged 0-2 years in Norway.

Methods: We used data from the Norwegian prescription database and included all dispensed prescriptions on systemic antibacterials in 2008-2017 during the first three years of life to children born 2005-2014. We calculated age by subtracting birth month and birth year from date of collection of prescription. We used multiple linear regression to investigate the effect of birth season on age at first dispensed prescription.

Results: We included 714 262 prescriptions to 281 888 individuals (53.1% boys). In 2016, one-year-old boys had the highest periodic prevalence (35.6%) and the highest dispense rate (545/1000 individuals), followed by one-year-old girls (32.6%, 478/1000 individuals). The lowest prevalence and dispense rate in all age groups was found towards the end of the period. Winter months had the highest proportion of dispensed prescriptions, and children born in autumn were significantly younger when collecting their first prescription. On average, boys collected their first prescription 26 days younger compared to girls.

Conclusion: One-year-olds have the highest periodic prevalence and the highest dispense rate. This contrast with results from other studies on Norwegian data and is probably attributed to our use of birth month for calculation of age. Children born in autumn were younger when collecting their first prescription compared to other birth seasons. It is unknown whether this has any long-term clinical implications.

INTRODUCTION

In 2017, there were > 800 000 consultations for children aged 0-5 years at general practitioners or emergency rooms in Norway. Among these, 34% were diagnosed with a respiratory tract infection (RTI) (1). In 2017, phenoxymethylpenicillin, Penicillin V (PcV), a common RTI antibacterial, was the most frequently dispensed drug in the age group 0-17 years in Norway (2). On the other hand, less than 30% of upper RTIs and radiological verified pneumonia in children < 5 years presumably have bacterial etiology (3,4).

In Norway in 2017, sex- and age specific one-year prevalence on dispensing of antibacterials was highest for children of 2 years, where 24% of girls and 27% of boys received at least one prescription (2). In Denmark in 2012, there were similar patterns with the highest incidence rate among those < 2 years, and the highest periodic prevalence among those 0-1 year, followed by the age group 2-4 years (5).

A recent Danish study investigated the association between birth season and age at first dispense of antibacterials and overall dispensing of antibacterials. The study included children born in 2004-2012 and showed a seasonally varying risk for receiving an antibacterial drug conditional on age. For example, children born in fall had at six months, a 4.9 percent point higher risk having received an antibacterial compared to children born in spring (6).

The high use of antibacterials in young children is of concern due to emerging antimicrobial resistance, and changes in the gut microbiota early in life, possibly associated with increasing risk for chronic diseases later in life (7–10). The national strategy to curb development of antibacterial resistance seek to reduce the overall consumption of antibacterial agents, with a special focus on broad-spectrum agents (11). The strategy aims to reduce antibacterial use by 30% from 2012 to the end of 2020, targeting unnecessary or irrational prescribing to children receiving antibacterials for RTIs of viral etiology.

The aim of this study is to describe the dispensing rate and one-year periodic prevalence of systemic antibacterials to children aged 0-2 years in Norway in the period 2008-2017, and to explore if there is an association between birth season and age at first redeemed prescription for antibacterials.

MATERIAL AND METHODS

Data were from the Norwegian prescription database (NorPD). Details on NorPD is described elsewhere (12).

We used the following variables from NorPD: sex, year of birth, month of birth, unique personal identifier

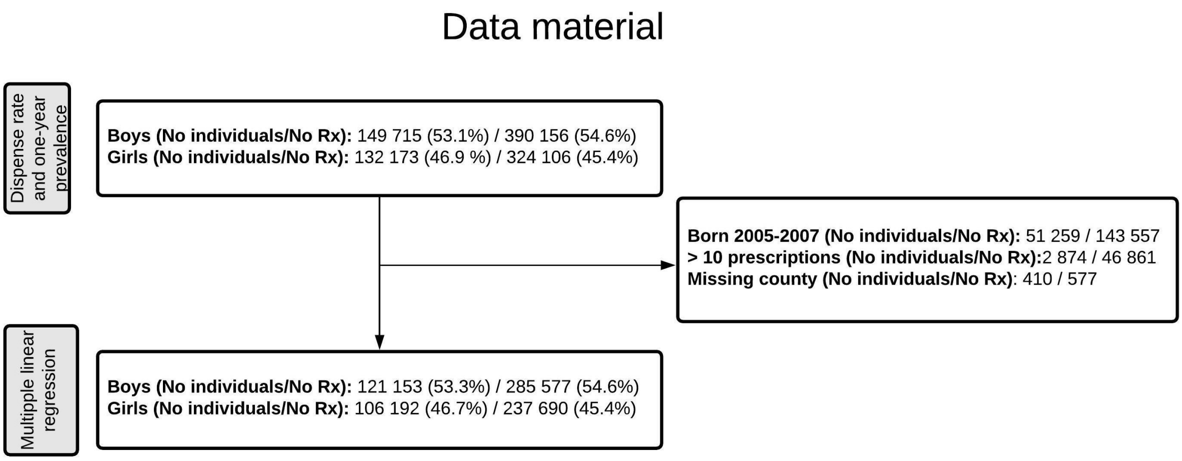

Figure 1. Study flow diagram.

(ID), county of residence, date for redeemed prescription from pharmacy and ATC-code on fifth level.

Our data material consists of all prescriptions on ATC code J01 with a valid ID and month of birth from 2008-2017 to children born in 2005-2014. We excluded records for individuals > 1095 days (3 years), and those who died during the observation period. In addition, we aggregated prescriptions if an individual had received two or more prescriptions on the same antibacterial drug (ATC level 5) on the same date, as we considered them as the same treatment episode. Population statistics was obtained from Statistics Norway (SSB).

Analysis

Our data material contains information on birth month, but not date of birth. Consequently, we assigned a fictitious birth date of the 15th of their birth month, and age was calculated as date of dispense minus this date.

We calculated the annual sex specific dispense rate for use of antibacterials from 2008-2017. We also calculated the one-year periodic prevalence of children having received at least one prescription in each calendar year, and used population statistics on January 1st each year as the denominator.

Furthermore, to investigate the effect of birth season on age at firstly dispensed prescription, we used a multiple linear regression model including children born in 2008-2014. We excluded prescription records to those born in 2005-2007 as we could not fully capture the outcome variable (age at first dispensed prescription) during this period. We further excluded those receiving more than 10 prescriptions during their first three years of life and those without a valid county (Fig. 1). Variables included in the regression analysis were based on a literature review and available data. Directed acyclic graphs (DAGs) were used to visualize the causal structure of the model. In addition to birth season, we included sex, birth year and county of residence. A geographical dummy variable identified the three counties with the highest dispensing rate, and the three with the lowest in 2014. These were respectively Nord-Trøndelag, Akershus and Vestfold, and Finnmark, Troms and Telemark. We used the remaining 13 counties as reference.

The other reference categories in the regression model were fall as birth season, birth year 2008, and female sex. All variables were included as categorical variables as they did not comply with the requirement of linearity between outcome and independent variables.

Data management and ethics

All calculations were performed using SPSS version 27 and STATA version 15.

The project was approved by Regional Committees for Medical and Health Research Ethics (REK) and was considered to be within the purpose of the NorPD, and was approved according to registry legislation (13).

RESULTS

The data contains dispensed systemic antibacterials from Norwegian pharmacies in the period 2008 to 2017, for children born in 2005 to 2014. In the period 714 262 prescriptions were dispensed of which 53.7% were to boys. The records include dispensed prescriptions to 281 888 individuals of which 53.1% were boys (Fig. 1). Table 1 shows some characteristics of our data. The number of individuals in birth year 2005, 2006 and 2007 differs from the other birth years, due to the observation time only starting in 2008. Earlier dispensed prescriptions to these individuals are not captured in our data. Most children received only one prescription during their first three years of life (44.8-45.7%).

The dispense rate was higher in boys compared with girls for all age groups. 1-year-olds had the highest dispense rate, followed by 2-year-olds. The overall highest dispense rate was in 2010 with 502 per 1000. In the same year, the rate was 763 and 665 per 1000 respectively, for 1-year old boys and girls (Fig. 2). There has been a fall in total dispense rate since 2012, apart from a small rise in 2014 and 2016. 2016 does not

Table 1. User characteristics.

	Birth season	Spring		Summer		Autumn		Winter	
	No. individuals (No. Rx total)	*71 788 (182 365)*		*76 947 (194 955)*		*69 224 (173 343)*		*63 929 (163 599)*	
Variables		**No.**	**Proportion (%)**	**No.**	**Proportion (%)**	**No.**	**Proportion (%)**	**No.**	**Proportion (%)**
Sex	Male	38256	53.3	40963	53.2	36850	53.2	33673	52.7
	Female	33532	46.7	36011	46.8	32374	46.8	30256	47.3
Birth Year	2005	654	0.9	1071	1.4	1343	1.9	624	1.0
	2006	3999	5.6	5115	6.6	5339	7.7	3225	5.0
	2007	7312	10.2	8289	10.8	7769	11.2	6519	10.2
	2008	8925	12.4	9091	11.8	8222	11.9	8091	12.7
	2009	9422	13.1	9679	12.6	8963	12.9	8468	13.2
	2010	9145	12.7	9658	12.6	8760	12.7	8311	13.0
	2011	8684	12.1	9008	11.7	7763	11.2	7648	12.0
	2012	8130	11.3	8788	11.4	7364	10.6	7356	11.5
	2013	7975	11.1	8373	10.9	7042	10.2	6947	10.9
	2014	7542	10.5	7875	10.2	6659	9.6	6740	10.5
Geography	Low rate counties	4442	6.2	4567	5.9	4251	6.1	3921	6.1
	High rate counties	14100	19.6	14978	19.5	13204	19.1	12147	19.0
	Reference counties	53124	74.0	57288	74.5	51668	74.6	47745	74.7
	Missing	122	0.2	114	0.1	101	0.1	116	0.2
Average No. Rx		2.4	NA	2.4	NA	2.4	NA	2.4	NA
No. Rx first three years of life	1	32194	44.8	34451	44.8	31638	45.7	28797	45.0
	2	17197	24.0	18380	23.9	16525	23.9	15347	24.0
	3	9193	12.8	9876	12.8	8705	12.6	8103	12.7
	4	5188	7.2	5505	7.2	4800	6.9	4515	7.1
	5	2972	4.1	3272	4.3	2814	4.1	2649	4.1
	6	1717	2.4	1960	2.5	1625	2.3	1577	2.5
	7	1138	1.6	1131	1.5	1068	1.5	968	1.5
	8	695	1.0	745	1.0	599	0.9	584	0.9
	9	425	0.6	477	0.6	391	0.6	397	0.6
	10	291	0.4	289	0.4	280	0.4	254	0.4
	>10	778	1.1	861	1.1	779	1.1	738	1.2
Average age (days) at first Rx		558.7	NA	539.5	NA	531.5	NA	545.9	NA
Type of antibacterials (No. Rx)	Amoxicillin	44121	24.2	48125	24.7	42288	24.4	39444	24.1
	Penicillin V	77388	42.4	80807	41.4	72287	41.7	67985	41.6
	Erythromycin	28417	15.6	30277	15.5	26318	15.2	25454	15.6
	Other	32439	17.8	35746	18.3	32450	18.7	30716	18.8

Rx: dispensed prescription
Low rate Counties: Finnmark, Troms, Telemark
High rate counties: Nord-Trøndelag, Akershus, Vestfold

contain dispense records for 0-year-olds, as no individuals were 0-years in 2016, being born latest in 2014.

The one-year periodic prevalence was highest for 1-year-olds for both boys and girls (Fig. 3). The one-year prevalence was over 40% in 1-year-old boys in 2008 and 2010-2012 but decreased until 2015. For girls, the highest periodic prevalence was approximately 38% in 2010 and 2012. The overall periodic prevalence decreased from 28.9% in 2008 to 24.4% in 2017.

In our data, the most dispensed antibacterial substances were Penicillin V (PcV), amoxicillin (AMX) and erythromycin (ERY) (Table 1). Over the period, the proportion of redeemed PcV prescriptions increased from 41% in 2008 to 48% in 2017, the total proportion of AMX and ERY decreased from 41% to 31%.

Most prescriptions were dispensed in winter months (December, January, and February), and was lowest in summer months (June, July and partly August). We further visualized the monthly proportion of children redeeming an antibacterial prescription in the first three years of life, stratified for birth season (Fig. 4). The snowflake shows when the respective birth seasons experience winter (defined as January). The figure

Figure 2. Sex and age specific dispense rate of antibacterial prescriptions in 2008-2017. Annual dispense rate included children aged 0-2 years in 2008-2015, 1- and 2-year-olds in 2016 and 2-year-olds in 2017.

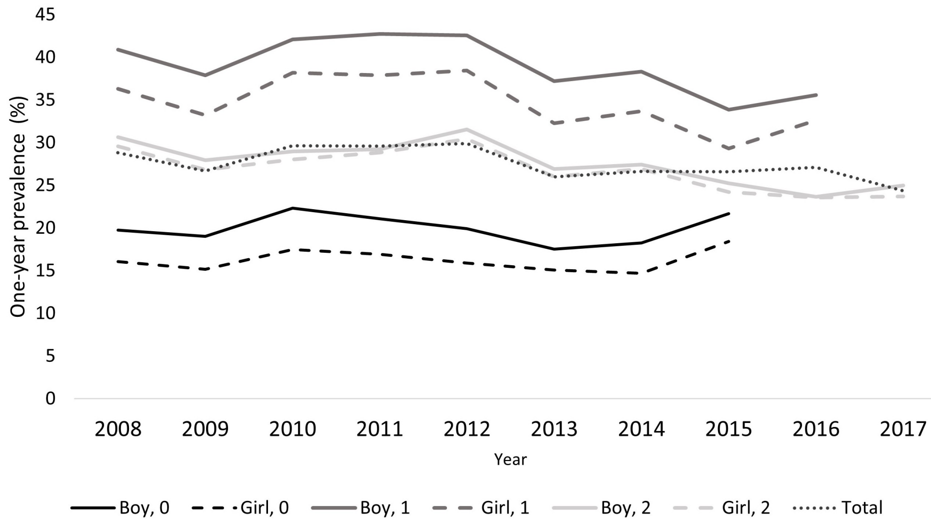

Figure 3. Sex and age specific one-year prevalence of antibacterial users (%) in 2008-2017. Annual one-year prevalence included children aged 0-2 years in 2008-2015, 1- and 2-year-olds in 2016 and 2-year-olds in 2017.

shows a cyclic order for all birth seasons, with a peak when the birth season experiences winter. For example, children born in spring (March-May) will experience winter in the age 8-10 months, 20-22 months, and 32-34 months, coinciding with the peak of proportion of redeemed prescriptions in all three periods. The same is observed for the other birth seasons.

Multiple linear regression

Our multiple linear regression analysis included 523 267 records to 227 577 individuals (53% boys). We excluded 143 557 prescription records to those born 2005-2007, 46 861 records to those receiving more than 10 prescriptions and 577 records with missing county (Fig. 1).

Table 2 shows the results of the multiple regression analysis, with age (in days) at first dispensed prescription as the outcome variable. The intersection in the regression analysis was 534 days for first dispensed prescription, representing the reference category, a girl born in fall of 2008 in one of the reference counties. The birth seasons spring, summer and winter, birth year 2009-2012, gender and dummy variables for counties were all significant covariates. Children born in autumn were significantly younger when redeeming their first prescription of an antibacterial agent, followed by summer, being 4 days older on average, winter (16 days older) and spring (22 days older). Boys had their first dispensed prescription 26 days younger compared to girls.

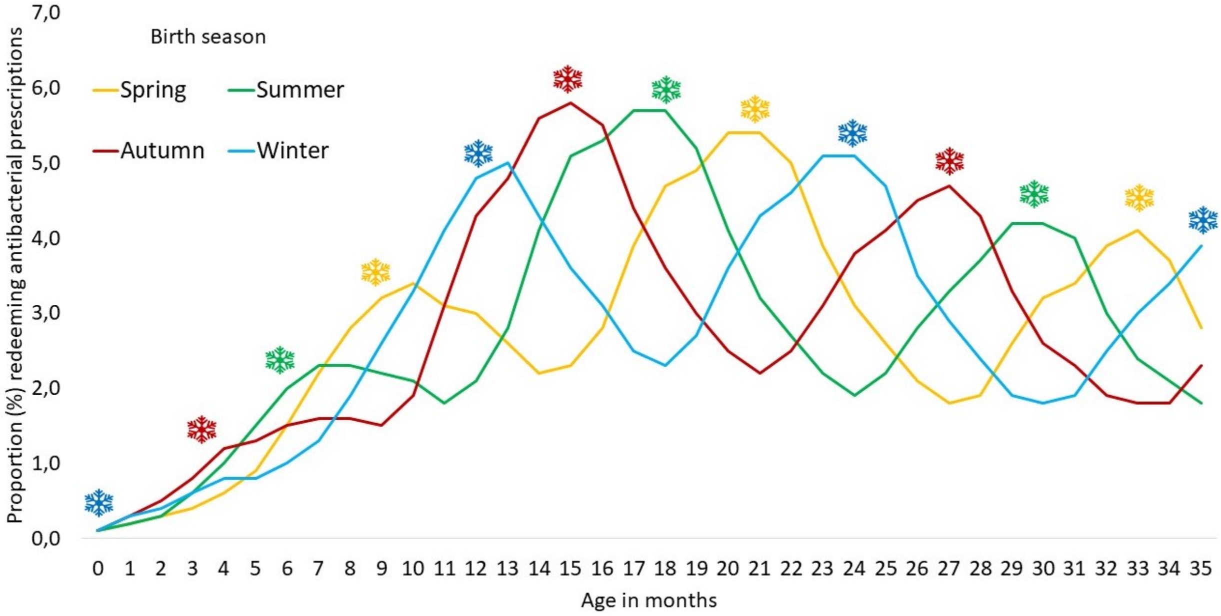

Figure 4. Proportion of children redeeming a prescription of antibacterials the first three years of life (0-35 months old), stratified by birth season. Snowflake indicates when the birth season experiences winter as period for redeeming a prescription.

DISCUSSION

In this nationwide drug utilization study, we describe dispense rate, periodic prevalence, and age at first dispensed prescription in children aged 0-2 years in Norway. Overall, we found a reduction in dispense rate for the years 2008-2017 for both girls and boys. The reduction was most pronounced in 2-year-olds. This trend is positive considering the goal of the national strategy of a 30% reduction from 2012 to the end of 2020 (11). The one-year periodic prevalence has also fallen over the period, but the decrease in dispense rate is more pronounced than the change in one-year prevalence, suggesting that the fall in proportion of users has changed less than the number of prescriptions per child. Almost half the children received only one prescription during their first three years of life, suggesting a restrictive use in this age group. We found a higher dispense rate of antibacterials for boys in all age groups, although the sex difference decreased for 2-year-olds. Some studies suggest that this may be due to sex differences such as higher incidence of acute otitis media in boys (14,15).

Since 2008 we have seen several events that could affect the dispense rate. For example, updates of national guidelines for use of antibacterials in primary health care (16–18), the KUPP campaign (Norwegian Prescription Peer Academic Detailing intervention) (19,20), ENORM (Educational intervention in NORwegian Municipalities for antibiotic treatment in line with guidelines) (21), and the publication of the national strategy against antibiotic resistance (11). Another Norwegian study showed a reduced relative risk for both acute otitis media and lower respiratory tract infections after the introduction of the 13-valent pneumococcal conjugate vaccine in the childhood vaccination program (22,23).

Table 2. Multiple linear regression analysis for age in days at first dispensed systemic antibiotics.

Variables	Beta	95% CI	P-value
Constant	533.7	526–533.4	
Birth season			
Fall	0 (ref.)		
Spring	21.9	19.1–24.9	**<0.001**
Summer	3.7	0.8–6.5	**0.011**
Winter	15.9	12.9–18.9	**<0.001**
Birth year			
2008	0 (ref.)		
2009	-5.9	(-9.5)–(-2.1)	**0.002**
2010	-14.3	(-17.8)–(-10.3)	**<0.001**
2011	-14.5	(-18.2)–(-10.7)	**<0.001**
2012	5.5	1.7–9.4	**0.005**
2013	-0.7	(-4.4)–3.3	0.705
2014	-2.8	(-6.3)–1.6	0.155
Gender			
Girl	0 (ref.)		
Boy	-26.2	(-28.3)–(-24.2)	**<0.001**
Geography			
Remaining counties	0 (ref.)		
Low rate counties	12.2	7.9–16.6	**<0.001**
High rate counties	-5.4	(-7.9)–(-2.7)	**<0.001**

Beta; unstandardized regression coefficient, CI; confidence interval
P-value calculated from multiple linear regression analysis
Reference: fall birth season, born 2008, girl, remaining counties.

Our study also shows that around 80% of all anti-bacterials dispensed were PcV, AMX and ERY (Table 1), all typical RTI antibacterials. This corresponds with RTIs being the single most common reason for children visiting a physician (1). We also observed an incline in use of PcV in line with quality indicators from the Norwegian Directorate of Health and current guidelines (18,24). However, the proportion of PcV is still lower than for Swedish children aged 0-6 years in 2017 (25).

The dispense rate has fallen since 2012, except for a small rise in 2014 for both boys and girls, 1- and 2-year-olds. This is in accordance with another Norwegian study using similar records from NorPD (26). The dispense rates in our analysis are low compared to similar studies from five European countries. A study from 2014 included data for 2008 from Denmark, Italy, Germany, Netherlands, and United Kingdom. In 2008 the dispense rate for Italian children 0-4 years was 1393 per 1000 person years, compared to the Netherlands having the lowest rate at 523 per 1000 (27). The rate in Norway were comparable to those in the Netherlands in 2008, where children 0-2 years redeemed 481 prescriptions per 1000 individuals.

Germany had a noticeably higher dispense rate compared to Denmark, Netherlands and Norway in 2008, but has since showed a reduction, particularly among children aged 0-5 years (28). Dispense rate was reduced from 2010 to 2018 in 0-1-year-olds from 630 to 320 per 1000, almost a 50% decrease. We observed around 34% decrease for 2-year-old boys and girls from 2008 to 2017, and a 25% decrease for 1-year-old boys and 21% decrease for 1-year-old girls from 2008 to 2016. The starting level in 2010 for German children were noticeably higher than Norwegian dispense rates, possibly allowing a greater relative reduction in rates. For example, in Germany children aged 0-1 year redeemed 630 prescriptions per 1000 persons, and 1212 per 1000 persons for children aged 2-5 years. The total number for dispensed prescriptions for children 0-2 years in Norway was in the same period 502 per 1000 individuals.

A more recent study from Hungary, Norway and Portugal identified antibacterial use as packages/child/year in 2014 with children age 0-19, stratified by age groups. This study identifies the youngest children (0-4 years) as the most frequent users of antibacterials, with respectively 2.2, 0.4 and 1.0 packages/child/year in Hungary, Norway and Portugal (29). The results from Norway are on par with our results, even though we are using different age stratification and proxy-measure for antibacterial use. This study misses the large variation for the age group 0-4 years that we have identified in our study.

Between 2008 and 2010 there were large fluctuations in dispensing rate (Fig. 2). There is a drop in 2009, and it has been speculated if this is associated to the H1N1-swine flu pandemic affecting Norway in the fall 2009 and improved hygiene measures during this period. This coincides with reduced contact rate for RTIs at the GPs and emergency rooms during the pandemic (30). A causal connection is still not clear.

We calculated age with a monthly fictitious birth date (set at the 15th). Several other studies on antibacterial use in children do not report method of age calculation. For example, three Norwegian studies have used data from NorPD to calculate age specific periodic prevalence (2,31,32). All identified the highest one-year periodic prevalence in 2-year-olds, and higher in boys than girls. These findings differ from ours, identifying 1-year-olds with the highest dispense rate and prevalence. Only one study gives information on definition of age, where year of dispensed prescription minus birth year is used. This has a margin of error of almost a year, whilst our method has a margin of error of maximum 16 days. Danish researchers used similar register data for the period 2000-2012, where age was calculated like our method. The results coincided with our results, identifying 1-year-olds with the highest dispense rate, followed by 2-year-olds, and the same for periodic prevalence (5). Calculating age with a low margin of error adds information value and indicates that aggregating age in larger age groups leads to substantial loss of information. For small children it can be of value to define age more specific than using year of birth, given that dispense rate and prevalence changes rapidly over a short time.

Our results show that a significantly higher number of prescriptions are dispensed in the winter months. Large variations in seasonality for use of antibiotics increasingly occur amongst those with high consumption (33), and possibly suggests suboptimal treatment. Fig. 4 also shows this trend. Winter season seems to be a predictor for if and when a child receives antibacterial treatment. All birth seasons show cyclic fluctuations with a peak when the birth season experience winter.

In the multiple linear regression analysis, we found an association between birth season and average age in days at first dispensed prescription. Our hypothesis was that children born in the fall would on average be younger when receiving their first dispensed prescription. These assumptions were congruent with the estimates from our analysis. However, the difference was moderate, but smallest for children born in summer, only being on average 3-4 days older at first dispensed prescription. There was a larger difference in average age for sex, girls being 26 days older on average on the first dispensed prescription. The results match that boys have a higher dispense rate and one-year prevalence generally at 0-2 years old (Figs. 2,3).

Kinlaw et al. used a Kaplan-Meier analysis to estimate the risk for receiving an antibacterial agent in the first year of life in Danish children (6). The authors reported a risk dependent partly on age. These results are comparable to our results (Fig. 4). Due to some differences in definition, we saw the highest proportion in dispensed prescriptions amongst children born in summer at 6 months old, but the peak for dispensed antibacterials was found to be February in Kinlaw's study, and January in ours.

It is difficult to decide whether differences in age at first dispensed prescription is of clinical relevance, and this should be explored with other study designs with access to clinical data and microbiome data. Even though all included covariates were significant in predicting the outcome, it is important to acknowledge the complexity underlying prescribing of antibacterials in young children. None of the included variables in our regression analysis is sufficient nor necessary factors for prescribing antibacterials in children.

Strengths and limitations

Data in NorPD are considered valid as law requires registration, it minimizes selection bias, data is unaffected by recall- or information bias, and gives almost complete data. We also had data from a long period in time, which allowed us to describe temporal trends in use. We have only included records with a valid patient ID. This was necessary to follow individuals over time and explore the number of prescriptions dispensed in their first three years of life, and to explore the effect of birth season on age at first dispensed prescription. Excluding those without ID may imply some selection bias, as the proportion of records without ID was highest early in the study period, and most noticeable for the youngest children (0-year-olds). This may contribute to some underestimation in dispense rate and one-year prevalence. Records without an ID normally represents those without a national identity number, such as new-borns, tourists or immigrants.

To avoid overestimating dispense rate, we aggregated prescriptions to individuals having received two or more prescriptions on the same day on the same antibacterial agent. Possibly, we should also have investigated change in therapy 1-3 days after the first dispense. A recent Norwegian study found that 2-year-old children most frequently received a new prescription for liquid (2.7%) and solid antibacterials (10.7%) (34), suggesting that dispense rate may still be overestimated.

Another weakness is the method of data extraction. We measured outcome for the period 2008-2017, and this includes children born in 2005-2014. This means that our newest data unfortunately only contains data for 2-year-olds. We chose this approach to be able to observe each child for a full three years of life. Consequently, individuals being born in 2005-2007 had to be excluded in the multiple regression, as we could not capture the outcome variable with certainty.

Another weakness to consider with register data is the lack of information on use in hospitals, or supply directly from prescriber. Possibly, direct supply from prescriber is more frequent in places with long distances to pharmacies. On a national level, it is unlikely that this would affect our estimates. We decided to aggregate counties into dummy variables in our multiple regression model, this leads to loss of information, but reduces the complexity of the analysis. It does not account for those who moved county or abroad at a later time. Geographical variation is most likely more complex than residence county can capture. A Norwegian study showed that antibacterial dispense declined with increasing latitude along the South-North axis, and was contingent on municipality population size (35).

A study from the Norwegian Neonatal Network assessed early sepsis and use of systemic antibacterials in infants. The authors reported that 6% of term born infants was admitted to hospital during their first week of life, and 39% of these received intravenous antibacterials, equivalent to 23 per 1000 term born infants in Norway (36). This suggest a slight overestimation of age at first dispensed prescription in our multiple linear regression, and may possibly give a small selection bias, because of the exclusion of the youngest and sickest infants being treated in hospital.

CONCLUSION

Our study identified an association between birth seasons and subsequently dispensed antibacterials. Winter as a dispensing season was a predictor for if and when a child received an antibacterial drug. Children born in autumn collected their first prescription at a younger age than the other birth seasons. Further studies should include clinical variables and microbiome data to explain the variance in time to first dispensed prescription and possible consequences of early use of antibacterials.

Children aged 0-2 years are among the most frequent users of antibacterials in Norway, and both dispense rate and prevalence has fallen over the period. 1-year-olds had the highest dispense rate and prevalence. We have identified large variation in age-specific rates, showing that aggregating the youngest children into wider age groups lead to loss of information.

This paper is based on a master's thesis from UiT the Arctic University of Norway, 2019:
Sanna Beckstrøm: Bruk av antibakterielle midler blant barn 0-3 år etter fødselssesong og fødselsår i Norge 2004-2017.

REFERENCES

1. Statistisk Sentralbyrå. Konsultasjoner hos fastlegen, etter alder, kjønn og diagnose. Tabell: 10141. Legevakt-konsultasjoner, etter alder, kjønn og diagnose. Tabell: 10903 [Internet]. Vol. 06.02.18. SSB; Available from: https://www.ssb.no/statbank/list/fastlegetj.
2. Furu K, Hjellvik V, Hartz I, Karlstad Ø, Skurtveit S, Blix HS, et al. Legemiddelbruk hos barn og unge i Norge 2008-2017. [Use of prescription drugs in children and adolescents in Norway 2007-2016]. Rapport 2018. Oslo: Folkehelseinstituttet; 2018.

3. Kronman MP, Zhou C, Mangione-Smith R. Bacterial prevalence and antimicrobial prescribing trends for acute respiratory tract infections. *Pediatrics* 2014;**134**(4):e956–65.
4. Berg AS, Inchley CS, Aase A, Fjaerli HO, Bull R, Aaberge I, et al. Etiology of pneumonia in a pediatric population with high pneumococcal vaccine coverage: A prospective study. *Pediatr Infect Dis J* 2016;**35**(3):e69-75.
5. Pottegård A, Broe A, Aabenhus R, Bjerrum L, Hallas J, Damkier P. Use of antibiotics in children: A Danish nationwide drug utilization study. *Pediatr Infect Dis J* 2015;**34**(2):e16–22.
6. Kinlaw AC, Stürmer T, Lund JL, et al. Trends in antibiotic use by birth season and birth year. *Pediatrics* 2017;**140**(3):e20170441.
7. Korpela K, de Vos WM. Antibiotic use in childhood alters the gut microbiota and predisposes to overweight. *Microb Cell* 2016;**3**(7):296–8.
8. Mårild K, Ye W, Lebwohl B, Green PHR, Blaser MJ, Card T, et al. Antibiotic exposure and the development of coeliac disease: a nationwide case-control study. *BMC Gastroenterol* 2013;**13**:109.
9. Risnes KR, Belanger K, Murk W, Bracken MB. Antibiotic exposure by 6 months and asthma and allergy at 6 years: Findings in a cohort of 1,401 US children. *Am J Epidemiol* 2011;**173**(3):310–8.
10. Dydensborg Sander S, Nybo Andersen AM, Murray JA, Karlstad Ø, Husby S, Størdal K. Association between antibiotics in the first year of life and celiac disease. *Gastroenterology* 2019;**156**(8):2217–29.
11. Helse- og omsorgsdepartementet. Nasjonal strategi mot antibiotikaresistens 2015-2020 [National Strategy against Antibiotic Resistance]. Oslo; 2015. Available from: https://www.regjeringen.no/contentassets/5eaf66ac392143b3b2054aed90b85210/strategi_antibiotikaresistens_230615.pdf.
12. Furu K. Establishment of the nationwide Norwegian Prescription Database (NorPD) – new opportunities for research in pharmacoepidemiology in Norway. *Norsk Epidemiologi* 2009;**18**(2):129–36. Available from: https://doi.org/10.5324/nje.v18i2.23.
13. Forskrift om reseptregisteret. Forskrift om innsamling og behandling av helseopplysninger i Reseptbasert legemiddelregister (Reseptregisteret), (FOR-2003-10-17-1246). 2003. Available from: https://lovdata.no/dokument/SF/forskrift/2003-10-17-1246.
14. Todberg T, Koch A, Andersson M, Olsen SF, Lous J, Homoe P. Incidence of otitis media in a contemporary Danish National Birth Cohort. *PLoS One* 2014;**9**(12):e111732.
15. Nystad W, Håberg SE, London SJ, Nafstad P, Magnus P. Baby swimming and respiratory health. *Acta Paediatr* 2008;**97**(5):657–62.
16. Berild D, Digranes A, Hjortdahl P, Von der Lippe E, Melby H, Ringertz S. Smittevernloven – Håndbok: antibiotikabehandling i allmennpraksis. Oslo: Statens helsetilsyn; 2000. Available from: https://urn.nb.no/URN:NBN:no-nb_digibok_2008100104041.
17. Eliassen KE, Fetveit A, Hjortdahl P, Berild D, Lindbæk M. Nye retningslinjer for antibiotikabruk i primærhelsetjenesten [New guidelines for use of antibiotics in the primary health care service]. *Tidsskr Nor Legeforen* 2008;**128**(20):2330–4.
18. Antibiotikasenteret for primærmedisin (ASP) og Helsedirektoratet. Nasjonale faglige retningslinjer for antibiotikabruk i primærhelsetjenesten. Oslo: Helsedirektoratet; 2020. Available from: https://www.helsedirektoratet.no/retningslinjer/antibiotikabruk-i-primaerhelsetjenesten.
19. Langaas HC, Dyrkorn R, Giverhaug T. Kunnskapsbaserte oppdateringsvisitter. Riktigere bruk av antibiotika. *Utposten* 2016;**45**(1):54–5. Available from: https://relis.no/content/4698/KUPP--Kunnskapsbaserte-oppdaterings-visitter.-Riktigere-bruk-av-antibiotika.
20. Gjelstad S, Hoye S, Straand J, Brekke M, Dalen I, Lindbaek M. Improving antibiotic prescribing in acute respiratory tract infections: cluster randomised trial from Norwegian general practice (prescription peer academic detailing (Rx-PAD) study). *BMJ* 2013;**347**:f4403.
21. Sunde M, Nygaard MM, Høye S. General practitioners' attitudes toward municipal initiatives to improve antibiotic prescribing – A mixed-methods study. *Antibiotics* 2019;**8**(3):120.
22. Folkehelseinstituttet. Pneumokokkvaksine – veileder for helsepersonell. Oslo: FHI. Available from: https://www.fhi.no/nettpub/vaksinasjonsveilederen-for-helsepersonell/vaksiner-mot-de-enkelte-sykdommene/pneumokokkvaksinasjon---veileder-fo/.
23. Magnus MC, Vestrheim DF, Nystad W, Haberg SE, Stigum H, London SJ, et al. Decline in early childhood respiratory tract infections in the Norwegian mother and child cohort study after introduction of pneumococcal conjugate vaccination. *Pediatr Infect Dis J* 2012;**31**(9):951–5.
24. Helsedirektoratet. Kvalitetsindikatorer – Antibiotikabehandling ved luftveisinfeksjoner hos barn mellom 0-9 år. Helsedirektoratet, Reseptregisteret. Available from: https://helsenorge.no/Kvalitetsindikatorer/legemidler.
25. Swedres-Svarm 2017. Consumption of antibiotics and occurrence of resistance in Sweden. Solna/Uppsala ISSN1650-6332; Available from: https://www.sva.se/globalassets/redesign2011/pdf/om_sva/publikationer/swedres_svarm2017.pdf.
26. Størdal K, Mårild K, Blix HS. Bruk av antibiotika hos barn i perioden 2005-16. *Tidsskr Nor Legeforen* 2017;137(18). doi: 10.405/tidsskr.17.0272.

27. Holstiege J, Schink T, Molokhia M, Mazzaglia G, Innocenti F, Oteri A, et al. Systemic antibiotic prescribing to paediatric outpatients in 5 European countries: a population-based cohort study. *BMC Pediatr* 2014;**14**:174.
28. Holstiege J, Schulz M, Akmatov MK, Steffen A, Bätzing J. Marked reductions in outpatient antibiotic prescriptions for children and adolescents – a population-based study covering 83% of the paediatric population, Germany, 2010 to 2018. *Euro Surveill* 2020;**25**(31):1900599.
29. Benko R, Matuz M, Silva A, Ferreira J, Machado MC, Furtado C, et al. Cross-national comparison of paediatric antibiotic use in Norway, Portugal and Hungary. *Basic Clin Pharmacol Toxicol* 2019;**124**(6):722–9.
30. Sandvik H, Hunskår S. Hygienekampanjen høsten 2009 – færre infeksjonstilfeller på legevakt? *Tidsskr Nor Legeforen* 2011;**131**(7):680–2.
31. Blix HS, Engeland A, Litleskare I, Rønning M. Age- and gender-specific antibacterial prescribing in Norway. *J Antimicrob Chemother* 2007;**59**(5):971–6.
32. Skreosen S. Antibakterielle midler til systemisk bruk til barn i aldersgruppen 0-5 år i Norge og Emilia-Romagna [Master Thesis]. UiT Norges arktiske universitet; 2016. Available from: https://munin.uit.no.
33. Versporten A, Coenen S, Adriaenssens N, Muller A, Minalu G, Faes C, et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient penicillin use in Europe (1997-2009). *J Antimicrob Chemother* 2011;**66** Suppl 6:vi13-23.
34. Bergene EH, Nordeng H, Ro TB, Steinsbekk A. Requests for new oral antibiotic prescriptions in children within 2 days: a Norwegian population-based study. *Fam Pr* 2018;**35**(6):690–7.
35. Haugen P, Simonsen GS, Primicerio R, Furberg AS, Småbrekke L. Antibiotics to outpatients in Norway – Assessing effect of latitude and municipality population size using quantile regression in a cross-sectional study. *Pharm Stat* 2018;**17**(1):4–11.
36. Fjalstad JW, Stensvold HJ, Bergseng H, Simonsen GS, Salvesen B, Ronnestad AE, et al. Early-onset sepsis and antibiotic exposure in term infants: A nationwide population-based study in Norway. *Pediatr Infect Dis J* 2016;**35**(1):1–6.