Family Practice, 2018, 1–8
doi:10.1093/fampra/cmy033

OXFORD

Epidemiology

Requests for new oral antibiotic prescriptions in children within 2 days: a Norwegian population-based study

E H Bergene[a,b,*], H Nordeng[c,d], T B Rø[e,f] and A Steinsbekk[a]

[a]Department of Public Health and Nursing, NTNU – Norwegian University of Science and Technology, Trondheim, Norway, [b]Central Norway Hospital Pharmacy Trust, Trondheim, Norway, [c]PharmacoEpidemiology and Drug Safety Research Group, School of Pharmacy, University of Oslo, Oslo, Norway, [d]Department of Child Health and Development, Norwegian Institute of Public Health, Oslo, Norway, [e]Department of Clinical and Molecular Medicine, NTNU – Norwegian University of Science and Technology, Trondheim, Norway and [f]Department of Pediatrics, St Olav's Hospital, Trondheim, Norway.

*Correspondence to E H Bergene, Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, PO Box 8905, N-7491 Trondheim, Norway; E-mail: elin.h.bergene@ntnu.no

Abstract

Background. Children commonly refuse to take antibiotics, which may induce parents to request new antibiotic prescriptions with different pharmaceutical characteristics.
Objectives. To investigate prescription changes for children 0–12 years receiving oral liquid or solid antibiotic formulations and to explore the relationships between prescription changes and characteristics related to the child, prescriber and antibiotic.
Methods. A population-based registry study based on data from the Norwegian Prescription Database (NorPD) from 2004 to 2016. Antibiotic prescription changes were defined as the dispensing of subsequent antibiotics with different pharmaceutical characteristics to the same child within 2 days after initial prescriptions. Data were analysed using multivariable logistic regression and generalized estimating equations.
Results. Requests for new prescriptions followed 3.0% of 2 691 483 initial antibiotic prescriptions for children. Young children who received solid formulations (10.9%) and certain poor-tasting antibiotics (8.6%) had the highest proportions of new prescriptions. Penicillin V was most commonly changed, while macrolides/lincosamides dominated subsequent prescriptions. In order of magnitude, the characteristics associated with requests for new prescriptions were the children's ages, poor taste and concentration of liquids, size and shape of solids, prescribers born in recent decades, and girl patients. Reimbursed prescriptions and scored solids were associated with fewer requests.
Conclusions. While only 3% of the antibiotic prescriptions were changed, the preference of broad-spectrum over narrow-spectrum antibiotics for young children in this study mirrors international prescription patterns. Avoiding the costs of children's refusal and consequent changes may thus be a motivation for choosing more preferred antibiotics.

Key words: Anti-bacterial agents, child, preschool child, dosage form, prescriptions.

Introduction

Antibiotics are the most commonly prescribed medicines for children in Europe (1). Worldwide, the prescription of antibiotics per child-year is highest in children 5 years and younger (0.5–3.4) and lowest in children 6–12 years (0.2–0.8) (2). Administering antibiotics to children can be challenging, and French parents reported in a survey that their child spat out at least one dose of antibiotics in 22% of the cases (3). In a recent qualitative study, parents said they battled with unwilling children and used several strategies to administer unpalatable antibiotics (4). If unable to get the child to take the medicine, parents sometimes went to the trouble of requesting a new antibiotic prescription (4,5). Such requests represent situations of negative interaction between children and parents and may reduce children's well-being through treatment delay. Children are also at risk of increased side effects from second-line antibiotics (6). Parents spend time and money on unused antibiotics that later may be administered inappropriately (7), and health-care resources may be wasted in the form of extra time and effort by the prescriber and pharmacy. To better understand the magnitude and nature of this problem in clinical practice, studies exploring changes in antibiotic prescriptions are needed.

In a previous Danish study, 5% of <30 000 prescriptions were followed by a new prescription within 2 days for children 0–5 years (8), and a similar study found that penicillin V was changed 3.7 times more often than amoxicillin (9). The authors concluded that this could be caused by differences in palatability and found support for this in previous taste tests (10). In addition to taste, a survey of adolescents and parents of children with chronic diseases in Great Britain showed that formulation factors such as size, shape and volume as well as child's age were correlated with children's refusal of medicine (11). Prescriber characteristics may also be associated with use of medicines, as prescription patterns change based on a prescriber's experience (12,13). Identifying factors related to changed prescriptions can be used to discover trends and population preferences and can be used to cause awareness and design interventions. To some extent, this can be explored in clinical practice using data from entire populations provided by national registers, such as the Norwegian Prescription Database (NorPD) (14).

The aim of this study was therefore to investigate prescriptions of oral liquid and solid antibiotic formulations changed within 2 days to antibiotics with different characteristics in children 0–12 years of age in Norway during the period from 2004 to 2016. Furthermore, associations between prescription changes and child, prescriber and antibiotic characteristics were investigated separately for solid and liquid antibiotics.

Methods

Study design and data source

This is a population-based registry study based on data on all prescriptions of oral systemic antibiotics dispensed to children from 2004 to 2016 in the NorPD. Children aged 0–12 were included to explore changes of antibiotic prescriptions across age intervals when both liquid and solid formulations were common (15). The NorPD contains information for all prescription medicines, reimbursed or not, dispensed from Norwegian pharmacies since 1st January 2004 to all individual patients living outside institutions (14).

Setting

In Norway, systemic antibiotics are available by prescription only, and a physician must be contacted to obtain a new prescription. In the community setting, antibiotics are predominantly dispensed from pharmacies to patients. Exceptions are antibiotics dispensed directly to the patient from out-of-hours primary health care centres that stock a small quantity of medications for use when pharmacies are closed (16). Antibiotics are fully paid for by the child's parents, except for children with severe/chronic conditions (e.g. immunodeficiency, cancer, or chronic urinary tract infections), whose antibiotic prescriptions are reimbursed. Reimbursed prescriptions accounted for 3.5%–5.4% of the antibiotics prescribed for children below 12 years of age in 2012 (2).

Inclusion criteria

All systemic oral antibiotic prescriptions classified according to the Anatomical Therapeutic Chemical (ATC) Classification System as ATC-code J01 were included with the exception of the antiseptic methenamine (ATC-code J01XX05).

Changed antibiotic prescriptions

Changed antibiotic prescriptions were defined as initial prescriptions that were followed by subsequent prescriptions with a different type of antibiotic or pharmaceutical characteristic (e.g. taste, size, shape, or strength/concentration) dispensed to the same child within 2 days. This period was chosen, as changes within the first 2 days were most likely caused by challenges related to the administration of antibiotics rather than lack of clinical effect (17). Prescription change served as the dependent variable and was categorized as either 'yes' or 'no'.

Characteristics

Medication characteristics

Formulations were classified as liquid (mixtures, drops, powder, and dispersible tablets) or solid (tablets and capsules).

The shapes of solid formulations were categorized as a capsule, an oval/oblong or round tablet. Scored tablets with indented lines that ease splitting were an independent category.

To compare the size of solids of different shapes, the cross-sectional area was computed using the measurement of width (w) and length (l) and the geometric formula $(l - w)w + \pi (w/2)^2$. The sizes were categorized into four categories: small <20 mm^2 (area of a 5-mm round tablet), medium 20–<79 mm^2 (area of 10-mm round tablet), large 79–124 mm^2 (area of size 1 capsule) or extra-large >124 mm^2.

Information regarding the size, shape and scoring of the solids was obtained from the Scandinavian medicinal formularies (18–20), from pillbox (21), or directly from the pharmaceutical manufacturer *via* personal contact. For generic medications, no longer manufactured, size information was unavailable (1.7% of the prescriptions for solid antibiotics). These were assigned to the same size category as the original matching formulation (tablet or capsule).

Antibiotics were grouped according to the ATC system and their overall prescription frequency: Penicillin V (ATC-code J01CE02), macrolides/lincosamides (ATC-code J01F), amoxicillin (ATC-code J01CA04) and others.

Poor-tasting liquids included dicloxacillin, clindamycin, trimethoprim, co-amoxicillin and penicillin V, whose scores on taste tests were so low that the likelihood for rejection by children was a concern (10,22,23).

Drops were included as a separate variable, as the concentration of antibiotic liquids is believed to influence their use in children (24).

Child characteristics

Both gender and age were included. Age was grouped as infants (0–1 years), toddlers (2–3 years), preschool children (4–5 years), school children (6–9 years) and pre-teens (10–12 years).

Prescriber characteristics

Prescribers were classified according to age, specialization and annual prescribing frequency. Age was defined by decade of birth. Specialization was categorized as general practitioner (GP) specialist, paediatrician, other specialist or no specialization. GP specialists have previously shown different antibiotic prescription patterns than non-GP specialists (25), which may influence antibiotic prescription changes. The annual prescribing frequency was grouped into quartiles due to a highly skewed distribution.

Statistical analysis

Logistic regression was used to assess the relationship between the antibiotic prescription changes and the characteristics of the child, prescriber and antibiotic. As antibiotic prescriptions could be changed several times for the same child, we used generalized estimating equations nested by children to account for possible correlations. Antibiotic prescription changes over time were analysed using univariable models, including the prescription year. Two multivariable models, including children and prescriber characteristics and either formulation characteristics (Model 1) or antibiotic groups (Model 2), were analysed separately for liquid and solid initial formulations due to the collinearity between formulation characteristics and antibiotic groups. Infants were references for liquids and pre-teens for solids due to their common use in these groups.

The results from the univariable models were reported as odds ratios (OR) with a 95% confidence interval (95% CI), while multivariable models were reported as adjusted odds ratios (adjOR) with a 95% CI. *P* value of <0.01 was considered statistically significant.

Several sensitivity analyses were performed to assess the robustness of the findings. First, antibiotic change was extended to 3 days after the initial prescription. Second, analyses were performed to reduce the contribution from children with more than four prescriptions per year per child (4% of all prescriptions) and from missing data by excluding prescriptions in 2004 [the year with the most missing patient IDs (26)] and children below 1 year of age, as there may have been a delay in receiving a national ID number. In addition, as Furadantin® is registered as a tablet but may be dispersed before administration, a sensitivity analysis was performed categorizing it as a liquid.

The analyses were carried out using Stata version 13.1 (StataCorp, College Station, TX).

Results

The overall dataset consisted of 2 691 483 initial prescriptions of systemic antibiotics that were dispensed to children 0–12 years between 2004 and 2016 in Norway. Of these, 21 701 prescriptions were followed by new prescriptions on the same day (Day 0), 35 703 on Day 1 and 22 697 on Day 2, totaling 80 101 changed prescriptions (3.0%).

Multiple prescriptions dispensed on the same day were excluded from the analyses as the lack of dispensing order did not allow us to identify the initial and changed antibiotic (1.6%, n = 43 769 prescriptions in 21 701 changes). Changes on Day 1–2 were therefore used for the analyses. The remaining dataset consisted of 2 670 754 initial prescriptions (1 976 238, 74% liquid and 694 516, 26% solid) dispensed to 861 991 children. The initial prescriptions were issued by 29 901 prescribers, and 41% (12 277) of these prescribers changed one or more prescriptions over the 13-year study period.

Proportions and trends of antibiotic changes on Day 1–2

On Day 1–2, 58 400 (2.2%) prescriptions were changed, of which 42 434 (2.2%) were liquid and 15 966 (2.4%) were solid. The same prescriber issued both the initial and subsequent prescriptions in 45.9% of the cases. The proportion of prescription changes increased over time for solids but not liquids (10-year OR: 1.3 for solids and 1.0 for liquids) (Fig. 1a).

Children below the age of 7 had a higher proportion of changes following prescription of solids, whereas children above 7 years had a higher proportion of changes following liquids. Two-year-old children had the highest proportion of changes following both solids (10.9%) and liquids (2.7%) (Fig. 1b).

Among individual oral antibiotics with at least 5000 prescriptions, amoxicillin had the lowest proportion of changes for both liquids (0.8%) and solids (1.0%) (Table 1). The highest proportion of liquid prescription changes were for dicloxacillin (8.6%) and penicillin V drops (4.9%), and for solids, it was penicillin V (4.7%).

Characteristics associated with requests for new prescriptions following liquid antibiotics

In the multivariable models, changes associated with liquid antibiotic prescriptions were (in decreasing magnitude) as follows:

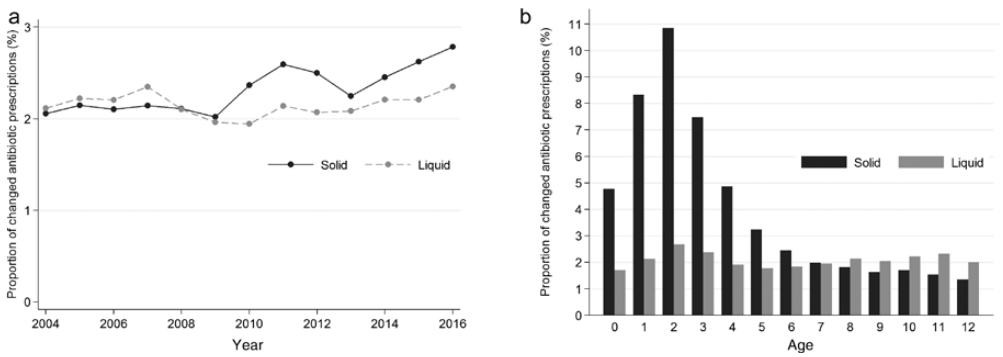

Figure 1. Proportion of antibiotic prescription changes on Day 1–2 (%) for solid and liquid formulations for (a) year 2004–16 and (b) age 0–12 years for 2.6 million prescriptions of oral antibiotics from the Norwegian Prescription Database.

Table 1. Top five individual liquid and solid antibiotics with the highest and lowest proportions of antibiotic change for prescriptions of oral antibiotics from the Norwegian Prescription Database between 2004 and 2016

Antibiotic	Formulation[a]	Initial prescriptions (*n*)	Antibiotic change (%)	Taste[b]/size[a]	Brand name
			Liquids most commonly changed		
Dicloxacillin	Suspension	8740	8.6	Poor	Diclocil® 12.5 mg/ml
Penicillin V	Drops/solution	19 378	4.9	Poor	Weifapenin® 250 mg/ml
Penicillin V	Drops/solution	174 336	4.0	Poor	Apocillin® 250 mg/ml
Penicillin V	Solution	170 714	3.5	Poor	Weifapenin® 50 mg/ml
Penicillin V	Solution	434 782	3.0	Poor	Apocillin® 50 mg/ml
			Liquids most seldom changed		
Amoxicillin	Solution	222 439	0.8	Not poor	Imacillin® 50 mg/ml
Amoxicillin	Solution	180 306	0.8	Not poor	Imacillin® 100 mg/ml
Cefalexin	Suspension	38 194	0.8	Not poor	Keflex® 50 mg/ml
Amoxicillin	Suspension	7617	0.9	Not poor	Amoxicillin® 100 mg/ml
Azitromycin	Suspension	61 249	1.0	Not poor	Azitromax® 40 mg/ml
			Solids most commonly changed		
Penicillin V	Oval/scored	29 985	4.7	Medium	Apocillin® 165 mg
Erythromycin	Oval	11 592	4.0	Extra-large	Abboticin® ES 500 mg
Erythromycin	Capsule	68 709	3.8	Large	Ery-Max® 250 mg
Dicloxacillin	Capsule	37 147	3.3	Large	Diclocil® 250 mg
Pivmecillinam	Round	23 494	3.3	Medium	Penomax® 200 mg
			Solids most seldom changed		
Amoxicillin	Round/scored	5982	1.0	Medium	Imacillin® 250 mg
Cefalexin	Oval/scored	5207	1.2	Large	Keflex® 500 mg
Amoxicillin	Capsule	10 534	1.2	Large	Amoxicillin®Mylan 250 mg
Azitromycin	Oval/scored	9962	1.3	Extra-large	Azitromax® 500 mg
Trimethoprim	Round/scored	11 272	1.3	Medium	Trimetoprim®Orion 100 mg

Only antibiotics with >5000 initial prescriptions included.

[a]Formulation and size (medium: 20–<79 mm^2, large: 79–124 mm^2, extra-large: >124 mm^2) based on information mainly from Scandinavian formularies (18–20).

[b]Taste according to taste test references by Steele *et al*. (10,22,23), where poor taste equals a score of 4 or less on a 10-point scale.

antibiotic taste, reimbursed prescriptions, drops, children's age, prescriber's birth decade and number of prescriptions issued per year, and gender (Table 2).

Compared with infants (0–1 years), prescriptions dispensed to toddlers (2–3 years) had the strongest association with prescription changes (adjOR: 1.3) followed by pre-teens (adjOR: 1.2) (Table 2). Reimbursed prescriptions dispensed to children with a chronic disease were least associated with changes (adjOR: 0.7). Girls had significantly higher odds than boys for prescription changes (adjOR: 1.07).

Younger prescribers were more strongly associated with changes compared with those born before 1950 (born after 1980, adjOR: 1.2).

The variables most strongly associated with a high number of prescription changes were antibiotics with a poor taste (adjOR: 2.4) and drops (adjOR: 1.5) (Table 2).

Characteristics associated with requests for new prescriptions following solid antibiotics

The prescriber characteristics associated with solid antibiotic prescription changes were quite similar to the prescriber characteristics of liquid antibiotic prescription changes; however, the difference in the association of changes between age groups was much greater for solids than liquids (Table 3).

Children below 4 years had almost eight times higher odds than pre-teens for changing a solid prescription. Prescriptions for both capsules and oval tablets were more strongly associated with prescription changes than round tablets (adjOR: 1.5 and 1.3, respectively), while scored tablets had a lower association (adjOR:0.6). There was also an influence of size, with extra-large solids having a stronger association with prescription changes (adjOR: 1.2) (Table 3).

Initial and subsequent antibiotic prescriptions

Of the initial prescriptions that were changed, penicillin V comprised the majority (58%) while amoxicillin was least commonly changed (6%) (Table 4). The macrolide/lincosamide group comprised most of the sequential prescriptions (36%). Of the initial macrolide/lincosamide antibiotics that were changed, 43% were followed by a subsequent prescription of a penicillin (penicillin V or amoxicillin).

The sensitivity analyses negligibly changed the results of the multivariable regressions (results not shown).

Discussion

Summary of the main findings

Requests for new prescriptions followed 3.0% of 2 691 483 initial antibiotic prescriptions for children. Young children who received solid formulations (10.9%) and certain poor-tasting antibiotics (8.6%) had the highest proportions of new prescriptions. Penicillin V was most commonly changed, while macrolides/lincosamides dominated subsequent prescriptions. In order of magnitude, the characteristics associated with requests for new prescriptions were as follows: the children's ages (solids), poor taste and concentration of liquids, size and shape of solids, prescribers born in recent decades, and girl patients. Reimbursed prescriptions and scored solids were associated with fewer requests.

Comparison with existing literature

Changed antibiotic prescriptions represent situations of parents in great distress, unable to get their child to take the medicine prescribed to get well (4). In addition, changes from narrow- to broad-spectrum

Table 2. Liquids: characteristics associated with liquid antibiotic formulations that were changed to a prescription with a different antibiotic or pharmaceutical characteristic from the Norwegian Prescription Database between 2004 and 2016

Liquid formulation					
Characteristics	Initial prescriptions (IP), *n* = 1 976 238	Subsequent prescriptions (% of IP)	Univariable OR (95% CI)	Model 1: Liquid characteristics	Model 2: Antibiotics
				Multivariable adjOR: (95% CI)	Multivariable adjOR: (95% CI)
Child					
Age group					
Infant 0–1 years	623 791	12 561 (2.0)	Reference	Reference	Reference
Toddler 2–3 years	640 816	16 277 (2.5)	**1.27 (1.24–1.30)**	**1.27 (1.24–1.30)**	**1.26 (1.23–1.29)**
Preschool 4–5 years	396 021	7335 (1.9)	**0.93 (0.90–0.95)**	**0.91 (0.88–0.93)**	**0.89 (0.87–0.92)**
School 6–9 years	274 862	5359 (2.0)	0.98 (0.95–1.02)	1.01 (0.97–1.04)	0.99 (0.96–1.02)
Pre-teen 10–12 years	40 748	902 (2.2)	**1.13 (1.06–1.22)**	**1.22 (1.14–1.31)**	**1.17 (1.09–1.26)**
Girl	962 148	20 926 (2.2)	1.03 (1.01–1.05)	1.02 (1.00–1.05)	**1.07 (1.05–1.09)**
Reimbursed AB	83 825	850 (1.0)	**0.46 (0.43–0.50)**	**0.53 (0.49–0.58)**	**0.66 (0.61–0.72)**
Prescriber					
Specialist					
None	974 765	23 082 (2.4)	Reference	Reference	Reference
GP	815 927	16 405 (2.0)	**0.85 (0.83–0.86)**	0.97 (0.94–0.99)	0.98 (0.96–1.01)
Paediatrician	98 565	1449 (1.5)	**0.65 (0.61–0.69)**	**0.92 (0.86–0.97)**	0.92 (0.87–0.98)
Other	86 981	1498 (1.7)	**0.73 (0.69–0.77)**	**0.92 (0.87–0.97)**	0.96 (0.91–1.01)
Birth year					
Before 1950	175 637	3215 (1.8)	Reference	Reference	Reference
1950–59	499 770	9300 (1.9)	1.01 (0.97–1.06)	1.02 (0.98–1.06)	1.02 (0.98–1.07)
1960–69	502 622	10 431 (2.1)	**1.13 (1.09–1.18)**	**1.07 (1.03–1.12)**	**1.08 (1.03–1.13)**
1970–79	572 659	13 565 (2.4)	**1.29 (1.24–1.35)**	**1.11 (1.07–1.16)**	**1.13 (1.08–1.18)**
After 1980	224 634	5903 (2.2)	**1.44 (1.37–1.50)**	**1.20 (1.14–1.26)**	**1.19 (1.13–1.25)**
Female prescriber	729 961	16 156 (2.2)	**1.05 (1.03–1.07)**	**0.97 (0.95–0.99)**	0.98 (0.96–1.00)
AB prescriptions per year (quartiles)					
<23	461 948	10 308 (2.2)	Reference	Reference	Reference
24–42	489 763	11 095 (2.3)	1.01 (0.99–1.04)	**1.06 (1.03–1.09)**	**1.07 (1.04–1.10)**
43–73	511 290	10 056 (2.2)	0.97 (0.94–0.99)	**1.08 (1.05–1.11)**	**1.09 (1.06–1.12)**
>73	513 237	9975 (1.9)	**0.87 (0.84–0.89)**	1.04 (1.01–1.07)	**1.07 (1.04–1.10)**
Liquid antibiotic					
Poor taste	968 756	29 954 (3.1)	**2.60 (2.55–2.66)**	**2.35 (2.30–2.41)**	
Drops	194 192	7986 (4.2)	**2.17 (2.12–2.23)**	**1.45 (1.41–1.49)**	
Antibiotics					
Amoxicillin	412 145	3229 (0.8)	Reference		Reference
Dicloxacillin	8740	756 (8.7)	**12.4 (11.4–13.5)**		**12.3 (11.3–13.4)**
Penicillin V	799 380	26 825 (3.4)	**4.55 (4.38–4.73)**		**4.52 (4.35–4.70)**
Clarithromycin	55 237	938 (1.7)	**2.22 (2.06–2.40)**		**2.34 (2.17–2.53)**
Erythromycin	358 940	6037 (1.7)	**2.21 (2.12–2.31)**		**2.24 (2.14–2.34)**
Clindamycin	49 524	821 (1.7)	**2.16 (1.99–2.34)**		**2.20 (2.03–2.39)**
Trim-sulpha	79 725	1271 (1.6)	**2.09 (1.95–2.24)**		**2.22 (2.07–2.38)**
Trimethoprim	107 010	1475 (1.4)	**1.82 (1.70–1.94)**		**1.93 (1.80–2.06)**
Azitromycin	61 249	614 (1.0)	**1.31 (1.20–1.44)**		**1.41 (1.28–1.55)**
Cefalexin	38 194	324 (0.9)	1.04 (0.92–1.18)		1.09 (0.96–1.24)

Multivariable models were also adjusted for the year the AB was dispensed. Only antibiotics with >5000 prescriptions are listed. Bold indicates $P < 0.01$.
AB, antibiotic; adjOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

antibiotics may increase children's short-term risk of side effects (6), and change of intestinal microbiome may result in future sequelae (27), furthering this distress. Changes also take parents' time away from the sick child to contact the prescriber and pharmacy and increase treatment costs for extra antibiotic courses. Surprisingly, girls experienced more prescription changes than boys, which is not explained by significant body size differences (28). Boys were generally more positive than girls towards taking oral formulations of different types and sizes in a recent study, indicating possible gender differences (29). Giving toddlers medicine may be extra difficult, as their proportion of change was higher than other age groups. This may be related to the increased use of broad-spectrum antibiotics in this age group, putting them at risk of antibiotic resistance (30). One explanation may be that prescribers choose more acceptable medicines to save time, as 41% of our prescribers had issued a new prescription (25). Prescribers born in recent decades changed more prescriptions, which may have contributed to the increase in prescription changes over the last 13 years. This effect remained after adjusting for type of antibiotics and warrants further exploration.

Poor-tasting liquid antibiotics had 2.4 times higher odds of being changed than better-tasting liquids. This corresponds with findings that taste is a key characteristic associated with children's refusal

Table 3. Solids: characteristics associated with solid antibiotic formulations that were changed to a prescription with a different antibiotic or pharmaceutical characteristic from the Norwegian Prescription Database (NorPD) between 2004 and 2016

Solid formulation					
Characteristics	Initial prescriptions (IP) *n* = 694 516	Re-prescriptions (% of IP)	Univariable OR (95% CI)	Model 1: Solid characteristics	Model 2: Antibiotics
				Multivariable adjOR: (95% CI)	Multivariable adjOR: (95% CI)
Child					
Age group					
Pre-teen 10–12 years	272 388	4156 (1.5)	Reference	Reference	Reference
School 6–9 years	313 042	6046 (1.9)	**1.28 (1.23–1.33)**	**1.40 (1.35–1.46)**	**1.38 (1.33–1.44)**
Preschool 4–5 years	74 159	2856 (3.9)	**2.61 (2.49–2.74)**	**3.06 (2.90–3.22)**	**3.13 (2.98–3.29)**
Toddler 2–3 years	26 107	2275 (8.7)	**6.25 (5.92–6.59)**	**7.86 (7.43–8.33)**	**8.25 (7.80–8.73)**
Infant 0–1 years	8820	633 (7.2)	**5.18 (4.74–5.67)**	**7.87 (7.16–8.66)**	**8.81 (7.99–9.71)**
Girl	380 566	8790 (2.3)	1.01 (0.98–1.05)	**1.06 (1.03–1.10)**	**1.06 (1.03–1.10)**
Reimbursed AB	35 778	510 (1.4)	**0.62 (0.57–0.68)**	**0.57 (0.52–0.63)**	**0.68 (0.61–0.76)**
Prescriber					
Specialist					
None (ref)	331 810	7935 (2.4)	Reference	Reference	Reference
GP	306 018	6980 (2.3)	**0.95 (0.92–0.99)**	1.05 (1.01–1.10)	1.04 (1.00–1.08)
Paediatrician	26 286	524 (2.0)	**0.86 (0.79–0.94)**	0.96 (0.87–1.06)	1.00 (0.91–1.11)
Other	30 402	527 (1.7)	**0.73 (0.66–0.79)**	**0.84 (0.77–0.92)**	0.90 (0.82–0.99)
Birth year					
Before 1950	67 823	1291 (1.9)	Reference	Reference	Reference
1950–59	192 050	4023 (2.1)	**1.10 (1.03–1.17)**	1.02 (0.96–1.09)	1.02 (0.96–1.09)
1960–69	172 782	3912 (2.3)	**1.19 (1.12–1.27)**	1.09 (1.02–1.16)	1.08 (1.01–1.15)
1970–79	184 484	4549 (2.5)	**1.30 (1.22–1.38)**	**1.16 (1.09–1.25)**	**1.15 (1.08–1.24)**
After 1980	77 011	2186 (2.8)	**1.49 (1.39–1.60)**	**1.26 (1.16–1.37)**	**1.25 (1.15–1.36)**
Female prescriber	240 884	5660 (2.3)	1.04 (1.00–1.07)	0.98 (0.95–1.02)	0.97 (0.94–1.01)
AB Prescriptions per year (quart)					
<23	208 436	4587 (2.2)	Reference	Reference	Reference
24–42	174 434	4139 (2.4)	**1.08 (1.04–1.13)**	**1.10 (1.05–1.15)**	**1.08 (1.04–1.13)**
43–73	166 187	3965 (2.4)	**1.09 (1.04–1.14)**	**1.15 (1.10–1.20)**	**1.13 (1.08–1.19)**
>73	145 459	3275 (2.3)	1.03 (0.98–1.08)	**1.14 (1.08–1.19)**	**1.13 (1.07–1.18)**
Solid antibiotic					
Shape					
Round	137 849	3023 (2.2)	Reference	Reference	
Oval	399 566	8090 (2.0)	**0.91 (0.88–0.95)**	**1.32 (1.25–1.39)**	
Capsule	157 101	4853 (3.1)	**1.40 (1.34–1.47)**	**1.50 (1.41–1.60)**	
Scored	418 047	7849 (1.9)	**0.63 (0.62–0.66)**	**0.64 (0.60–0.67)**	
Size					
20–<79 mm^2	360 892	7898 (2.2)	Reference	Reference	
79–124 mm^2	281 419	6887 (2.4)	**1.12 (1.08–1.16)**	1.06 (1.00–1.11)	
>124 mm^2	52 205	1181 (2.3)	1.04 (0.97–1.10)	**1.19 (1.10–1.28)**	
Antibiotic					
Amoxicillin	26 429	321 (1.2)	Reference		Reference
Erythromycin	80 309	3102 (3.9)	**3.25 (2.90–3.65)**		**3.92 (3.49–4.42)**
Dicloxacillin	55 097	1644 (3.0)	**2.50 (2.22–2.82)**		**2.22 (1.96–2.51)**
Clarithromycin	8971	169 (1.9)	**1.56 (1.29–1.88)**		**2.10 (1.74–2.54)**
Pivmecillinam	56 993	1780 (3.1)	**2.63 (2.33–2.96)**		**1.83 (1.62–2.08)**
Clindamycin	17 996	384 (2.1)	**1.76 (1.52–2.05)**		**1.76 (1.51–2.05)**
Penicillin V	355 262	7142 (2.0)	**1.67 (1.49–1.87)**		**1.50 (1.34–1.68)**
Azitromycin	9969	134 (1.3)	1.12 (0.91–1.37)		1.34 (1.09–1.64)
Doxycycline	5000	65 (1.3)	1.06 (0.81–1.38)		1.33 (1.01–1.75)
Trim-sulpha	14 964	210 (1.4)	1.18 (0.99–1.41)		1.26 (1.05–1.51)
Trimethoprim	22 510	305 (1.4)	1.13 (0.97–1.32)		1.17 (0.99–1.37)
Cefalexin	6 064	71 (1.2)	0.97 (0.75–1.26)		1.11 (0.86–1.44)
Nitrofurantoin	24 499	435 (1.8)	**1.49 (1.28–1.72)**		**0.61 (0.52–0.72)**

Multivariable models were also adjusted for the year the AB was dispensed. Only antibiotics with >5000 prescriptions are listed. Bold indicates $P < 0.01$.
AB, antibiotic; adjOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

Table 4. Initial oral solid and liquid antibiotics and subsequent prescriptions with different antibiotics or pharmaceutical characteristics (e.g. taste, size, shape, or strength/concentration) from the Norwegian Prescription Database between 2004 and 2016

Initial prescription		Subsequent prescription									
		Penicillin V		Macro/linco		Amoxicillin		Other		Form	
Antibiotic	Form (*n*)	Solid (6509)	Liquid (10 707)	Solid (4039)	Liquid (16 946)	Solid (790)	Liquid (10 512)	Solid (4062)	Liquid (4835)	Solid	Liquid
PenV, 58% (33 967)	Solid (7142)	2.3% (164)	42.5% (3038)	20.6% (1468)	15.5% (1108)	2.7% (196)	9.5% (677)	5.5% (395)	1.3% (96)	31.1% (2223)	68.9% (4919)
	Liquid (26 825)	17.9% (4813)	18.2% (4873)	0.8% (226)	34.0% (9151)	0.3% (76)	24.6% (6601)	0.5% (131)	3.6% (954)	19.6% (5246)	80.4% (21 579)
Macro/linco, 21% (12 235)	Solid (3789)	17.7% (669)	3.6% (136)	17.4% (661)	34.1% (1291)	5.8% (220)	3.8% (144)	15.8% (600)	1.8% (68)	56.7% (2150)	43.3% (1639)
	Liquid (8446)	6.7% (570)	19.6% (1652)	15.3% (1294)	24.3% (2056)	0.9% (72)	20.7% (1749)	2.9% (242)	9.6% (811)	25.8% (2178)	74.2% (6268)
Amoxicillin, 6% (3550)	Solid (321)	8.4% (27)	2.5% (8)	28.7% (92)	10.9% (35)	9.3% (30)	20.9% (67)	16.8% (54)	2.5% (8)	63.2% (203)	36.8% (118)
	Liquid (3229)	3.2% (103)	13.4% (434)	1.3% (42)	53.4% (1725)	3.4% (109)	4.6% (149)	4.1% (133)	16.5% (534)	12.0% (387)	88.0 % (2842)
Other, 15% (8648)	Solid (4714)	2.1% (100)	4.7% (223)	4.8% (228)	19.6% (926)	1.4% (66)	8.7% (408)	21.6% (1020)	37.0% (1743)	30.0% (1414)	70.0% (3300)
	Liquid (3934)	1.6% (63)	8.7% (343)	0.7% (28)	16.6% (654)	0.5% (21)	18.2% (717)	37.8% (1487)	15.8% (621)	40.6% (1599)	59.4% (2335)
All formulations	Total (58 400)	Total penV 29.5% (17 216)		Total macro/linco 35.9% (20 985)		Total amoxicillin 19.4% (11 302)		Total other 15.2% (8897)		26.4% (15 400)	73.6% (43 000)

PenV, penicillin V; Macro/linco, macrolides/lincosamides.

of medicines (31,32) and indicates that prescription changes can be used to identify antibiotics that are challenging for children to use. Changed prescriptions most likely underestimate administration challenges (4) and may contribute to the difference found in chronic children who were 3.8 times more likely to refuse poor-tasting medicines at least once (11). Taste may also explain why poor-tasting liquid penicillin V was most frequently replaced by better-tasting liquid amoxicillin and erythromycin, and even solid penicillin V that is easier to taste mask (33). Changes between liquid concentrations were seen for all the antibiotic groups. Concentrated liquids had 1.5 times greater odds of being changed, indicating that the advantage of having a smaller volume may not compensate for the stronger taste. The opposite was found in a study of children with chronic disease, although this was believed to be caused by an age factor (24).

There is little consensus in the literature regarding which size and shape solids to prescribe at different ages, but recent studies have shown that preschool children can swallow and even prefer mini tablets of 2–3 mm (34,35). There is a large discrepancy, though, between clinical studies and the availability of solids for clinical use (36). The two smallest solids in the dataset were 11 × 5 mm and 9 × 6.5 mm, which in a recent review would not be considered appropriate for children under 13 years (37). This is in keeping with the results in this study where younger children had stronger association with solid formulation changes, and medium and scored tablets had lower independent associations. Children can be taught to swallow solids (38), which may explain why this study showed that prescriptions reimbursed for children with a serious or chronic disease had lower odds for prescription changes.

Capsules had 1.5 times higher odds of prescription changes than round tablets, and erythromycin capsules were changed most frequently. This lack of preference for capsules may be explained by their large size and a misconception of being made from plastic (29). Erythromycin capsules, however, contain granules that can be sprinkled on food, making them easier to swallow (39), although this may not be known. Changes from penicillin V tablets to erythromycin were also seen (Table 4), which may indicate that opening the capsules may be known by some.

Strengths and limitations of the study

The strength of this study is the inclusion of prescriptions from the entire Norwegian paediatric population over a 13-year period. The two main limitations are lack of information regarding (i) the reason for requesting a new prescription and (ii) type and severity of infections. The prevalence of allergies and adverse effects is unknown and could contribute an overestimation of changes due to administration challenges. Though uncommon, more than one antibiotic could also have been prescribed on the same day intentionally, thus overestimating changes. Changes due to therapeutic failure could also overestimate the results, although the finding that more prescriptions were changed on Day 1 than on Day 2 indicates that this is unlikely to be a key factor.

Conclusion and implication

Changed prescriptions have costs for the involved children, their families and the health-care system in general. Narrow-spectrum antibiotics were changed more often than broad-spectrum antibiotics, indicating that costs related to children's refusal and consequent antibiotic changes may contribute to the increased prescription rates of broad-spectrum antibiotics observed for young children in general. Advocating the development of more user-friendly formulations for children can therefore contribute to a more appropriate use of antibiotics in the paediatric population.

Declaration

Funding: this study was funded by a grant from the Liaison Committee between the Central Norway Regional Health Authority and Norwegian University of Science and Technology (NTNU).

Ethical approval: the study was approved by the Regional Committee for Medical and Health Research Ethics, Central Region, ref 2014/1743, and the Norwegian Prescription Database, ref 17/10581. Patient and prescriber personal identification numbers were pseudonymized by NorPD, allowing individual children's prescriptions to be tracked over time without exposing their identities. The data were handled and stored anonymously.

Conflict of interest: none.

Acknowledgements

The authors would like to thank Eva Skovlund for support with the statistical analyses.

References

1. Sturkenboom MC, Verhamme KM, Nicolosi A *et al*. Drug use in children: cohort study in three European countries. *BMJ* 2008; 337: a2245.
2. Youngster I, Avorn J, Belleudi V *et al*. Antibiotic use in children—a cross-national analysis of 6 countries. *J Pediatr* 2017; 182: 239–244.e1.
3. Cohen R, de La Rocque F, Lecuyer A *et al*. Study of the acceptability of antibiotic syrups, suspensions, and oral solutions prescribed to pediatric outpatients. *Eur J Pediatr* 2009; 168: 851–7.
4. Bergene EH, Rø TB, Steinsbekk A. Strategies parents use to give children oral medicine: a qualitative study of online discussion forums. *Scand J Prim Health Care* 2017; 35: 221–8.
5. Brookes-Howell L, Wood F, Verheij T *et al*. Trust, openness and continuity of care influence acceptance of antibiotics for children with respiratory tract infections: a four country qualitative study. *Fam Pract* 2014; 31: 102–10.
6. Turck D, Bernet JP, Marx J *et al*. Incidence and risk factors of oral antibiotic-associated diarrhea in an outpatient pediatric population. *J Pediatr Gastroenterol Nutr* 2003; 37: 22–6.
7. Grigoryan L, Burgerhof JG, Haaijer-Ruskamp FM *et al*.; SAR group. Is self-medication with antibiotics in Europe driven by prescribed use? *J Antimicrob Chemother* 2007; 59: 152–6.
8. Thrane N, Olesen C, Schonheyder HC, Sorensen HT. Multiple prescriptions of antibiotics for children aged 0 to 5 years in relation to type of antibiotic. *J Antimicrob Chemother* 1999; 44: 839–42.
9. Pottegård A, Hallas J. Children prefer bottled amoxicillin. *Ugeskr Laeger* 2010; 172: 3468–70.
10. Steele RW, Estrada B, Begue RE, Mirza A, Travillion DA, Thomas MP. A double-blind taste comparison of pediatric antibiotic suspensions. *Clin Pediatr (Phila)* 1997; 36: 193–9.
11. Venables R, Batchelor H, Hodson J *et al*. Determination of formulation factors that affect oral medicines acceptability in a domiciliary paediatric population. *Int J Pharm* 2015; 480: 55–62.
12. Tell D, Engström S, Mölstad S. Adherence to guidelines on antibiotic treatment for respiratory tract infections in various categories of physicians: a retrospective cross-sectional study of data from electronic patient records. *BMJ Open* 2015; 5: e008096.
13. Gjelstad S, Dalen I, Lindbaek M. GPs' antibiotic prescription patterns for respiratory tract infections–still room for improvement. *Scand J Prim Health Care* 2009; 27: 208–15.
14. Furu K. Establishment of the nationwide norwegian prescription database (NorPD)–new opportunities for research in pharmacoepidemiology in Norway. *Norsk Epidemiologi* 2008; 18: 129–36.
15. Schirm E, Tobi H, de Vries TW, Choonara I, De Jong-van den Berg LT. Lack of appropriate formulations of medicines for children in the community. *Acta Paediatr* 2003; 92: 1486–9.
16. Rebnord IK, Thue G, Hunskår S. Equipment for diagnostics, laboratory analyses and treatment in out-of-hours services. *Tidsskr Nor Laegeforen* 2009; 129: 987–90.
17. Sanchez Garcia M. Early antibiotic treatment failure. *Int J Antimicrob Agents* 2009; 34 (suppl 3): S14–9.
18. Felleskatalogen. https://www.felleskatalogen.no/medisin/ (accessed 27 April 2018)
19. FASS. http://www.fass.se/LIF/ (accessed 27 April 2018).
20. Pro.medicin.dk. http://pro.medicin.dk/ (accessed 27 April 2018).
21. Pillbox. https://pillbox.nlm.nih.gov/ (accessed 27 April 2018).
22. Steele RW, Russo TM, Thomas MP. Adherence issues related to the selection of antistaphylococcal or antifungal antibiotic suspensions for children. *Clin Pediatr (Phila)* 2006; 45: 245–50.
23. Steele RW, Thomas MP, Bégué RE. Compliance issues related to the selection of antibiotic suspensions for children. *Pediatr Infect Dis J* 2001; 20: 1–5.
24. Rouse C, Mistry P, Rayner O *et al*. A mixed methods study of the administration of flucloxacillin oral liquid; identifying strategies to overcome administration issues of medicines with poor palatability. *Int J Pharm Pract* 2017; 25: 326–34.
25. Gjelstad S, Straand J, Dalen I, Fetveit A, Strøm H, Lindbæk M. Do general practitioners' consultation rates influence their prescribing patterns of antibiotics for acute respiratory tract infections? *J Antimicrob Chemother* 2011; 66: 2425–33.
26. Berg C, Blix HS, Fenne O *et al*. *Norwegian Prescription Database 2010–2014, in Statistics*. Oslo: Norwegian Institute of Public Health, 2015.
27. Korpela K, Salonen A, Virta LJ *et al*. Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children. *Nat Commun* 2016; 7: 10410.
28. Júlíusson PB, Roelants M, Eide GE *et al*. Growth references for Norwegian children. *Tidsskr Nor Laegeforen* 2009; 129: 281–6.
29. Ranmal SR, Cram A, Tuleu C. Age-appropriate and acceptable paediatric dosage forms: insights into end-user perceptions, preferences and practices from the Children's Acceptability of oral formulations (CALF) study. *Int J Pharm* 2016; 514: 296–307.
30. Holstiege J, Schink T, Molokhia M *et al*. Systemic antibiotic prescribing to paediatric outpatients in 5 European countries: a population-based cohort study. *BMC Pediatr* 2014; 14: 174.
31. European Medicines Agency. *Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012*. London: European Medicines Agency, 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf (accessed 25 April 2018).
32. Davies EH, Tuleu C. Medicines for children: a matter of taste. *J Pediatr* 2008; 153: 599–604, 604.e1–2.
33. Walsh J, Cram A, Woertz K *et al*.; European Formulation Initiative. Playing hide and seek with poorly tasting paediatric medicines: do not forget the excipients. *Adv Drug Deliv Rev* 2014; 73: 14–33.
34. van Riet-Nales DA, Ferreira JA, Schobben AF *et al*. Methods of administering oral formulations and child acceptability. *Int J Pharm* 2015; 491: 261–7.
35. Drumond N, van Riet-Nales DA, Karapinar-Çarkit F, Stegemann S. Patients' appropriateness, acceptability, usability and preferences for pharmaceutical preparations: results from a literature review on clinical evidence. *Int J Pharm* 2017; 521: 294–305.
36. Jacobsen L, Riley K, Lee B, Bradford K, Jhaveri R. Tablet/capsule size variation among the most commonly prescribed medications for children in the USA: retrospective review and firsthand pharmacy audit. *Paediatr Drugs* 2016; 18: 65–73.
37. Mistry P, Batchelor H; SPaeDD-UK project (Smart Paediatric Drug Development—UK). Evidence of acceptability of oral paediatric medicines: a review. *J Pharm Pharmacol* 2017; 69: 361–76.
38. Meltzer EO, Welch MJ, Ostrom NK. Pill swallowing ability and training in children 6 to 11 years of age. *Clin Pediatr (Phila)* 2006; 45: 725–33.
39. Nunn T, Williams J. Formulation of medicines for children. *Br J Clin Pharmacol* 2005; 59: 674–6.