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Use of topical ocular antibiotics in young children: a Scandinavian drug utilization study

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ABSTRACT.

Purpose: **Acute infectious conjunctivitis is a common disease. While usually self-limiting, children often receive treatment to be accepted back into nursery, day care or school. We aimed to describe trends in the utilization of topical ocular antibiotics in young children aged 0–4 years in Denmark, Norway and Sweden.**

Methods: **Using individual-level data from the Danish National Prescription Registry (2000–2015), we provided detailed descriptions of treatment patterns at the individual level, stratified by age (0–1 years, 2–4 years) and antibiotic substance. Aggregate-level data for Danish, Norwegian and Swedish children (0–4 years) were obtained from publicly available data sources (2000–2016).**

Results: **We identified 107 581 Danish children aged 0–4 years receiving 271 980 treatment episodes. The incidence rate was relatively stable between 2000 and 2010 (on average, 637 and 283/1000 person-years for 0- to 1- and 2- to 4-year-olds, respectively), after which it dropped by 37% until 2015. In the aggregated data, a markedly higher use was seen in Denmark (211/1000 children in 2016) compared with Sweden (42) and Norway (151). The decrease from 2010 onwards was observed in all three countries. Chloramphenicol and fusidic acid were the most commonly used topical ocular antibiotics across Scandinavia. Tobramycin was rarely used in Norway and Sweden (≤1/1000 children in 2016) compared with Denmark (24/1000 children).**

Conclusion: **Considerable variation is seen in the utilization of topical ocular antibiotics among children in Scandinavia, with Denmark having the highest use. Across the Scandinavian countries, however, a decline was noted from 2010 onwards.**

Key words: conjunctivitis – epidemiology – pharmacology – Scandinavia – topical ocular antibiotics

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Introduction

Acute infectious conjunctivitis is a very common eye disease that is primarily handled in primary care, where it is estimated to constitute approximately 1% of all consultations (Høvding 2008; Azari & Barney 2013). Every year, one in eight children has symptoms of acute conjunctivitis and the percentage is even higher among younger children (Høvding 2008). The majority of patients with acute conjunctivitis are treated by general practitioners rather than ophthalmologists (Azari & Barney 2013).

The difficulty in distinguishing between viral and bacterial conjunctivitis is a common problem (Høvding 2008; Sheikh et al. 2012; Azari & Barney 2013). In young children, 50–75% of acute conjunctivitis is caused by bacteria (Høvding 2008), while viral conjunctivitis is more common among adults (Azari & Barney 2013). Acute bacterial conjunctivitis is most often caused by *S. aureus*, while cases among young children are also frequently caused by *H. influenzae,* followed by *S. pneumoniae* and *M. catarrhalis* (Høvding 2008; Azari & Barney 2013). Viral conjunctivitis is often caused by adenovirus, *herpes simplex* virus or picornaviruses (Høvding 2008).

The majority of acute bacterial conjunctivitis cases are self-limiting and treatment is not required in uncomplicated cases (Høvding 2008; Azari & Barney 2013), as severe complications (keratitis) are rare (Høvding 2008). While topical ocular antibiotics may lead to a slightly more rapid clinical and microbiological remission of bacterial conjunctivitis, the majority of patients will recover spontaneously

without receiving treatment (Sheikh et al. 2012). Nevertheless, school and day care policies often dictate that children must receive antibiotic treatment before being allowed to return (Finnikin & Jolly 2016). Consequently, parents exert a substantial pressure on the medical doctor to obtain treatment for their child (Rose et al. 2006). This is reflected in the fact that topical ocular antibiotics are often prescribed to young children by telephone consultations, that is, without a clinical consultation (Huibers et al. 2014).

To promote rational use, there is a need for detailed information on prescription patterns of these drugs. Therefore, we aimed to describe the utilization of topical ocular antibiotics in Scandinavian children from 2000 to 2015.

Materials and Methods

We compared individual-level data on topical ocular antibiotics prescribed for all Danish children aged 0–4 years from 2000 through 2015 with aggregate statistics on topical ocular antibiotic use among children in Denmark from 2006 through 2016, in Norway from 2004 through 2016 and in Sweden from 2006 through 2016.

Data sources

Individual-level data were retrieved from the Danish National Prescription Registry (Pottegård et al. 2016), which covers individual-level information on prescribed medication dispensed from all community pharmacies to Danish residents since 1995. Among other variables, each record includes the substance, the date of purchase and a unique person identifier (Schmidt et al. 2014). The indication for the prescription is generally not available. Drugs are classified according to WHO's anatomical therapeutic chemical (ATC) system (Guidelines for ATC classification and DDD assignment 2016. Oslo, 2016 n.d.). The average number of children aged 0–4 years in the study period in Denmark was 346 486 (www.statistikbanken.dk).

Aggregate prescription data were retrieved from the public authorities. Danish data are publicly available at www.medstat.dk (Schmidt et al. 2016), Norwegian data at www.legemiddelforbruk.no and Swedish data at www.socialstyrelsen.se/statistik/statistikdatabas/lakemedel. These data sources hold data on wholesale (amount) drugs used as well as the 'annual period prevalence proportion', that is, the proportion of the population within a given age range that fills at least one prescription for a given drug or drug class in a given calendar year.

In all three countries, all antibiotics, regardless of route of administration, require a prescription from a medical provider.

Population and study drugs

For the individual-level analysis on Danish children, we identified all prescriptions of topical ocular antibiotics issued to a child aged ≤4 years (age at the time of filling the prescription). The age restriction of 0–4 years old was due to the fact that the highest use was observed in this group based on preliminary analyses of publicly available data obtained via Medstat.dk (Schmidt et al. 2016). We included prescriptions for all topical ocular antibiotics, defined as ATC groups S01AA (general antibiotics), S01AB (sulphonamides) and S01AE (fluoroquinolones) at both an individual and aggregate level. For the remainder of the manuscript, the term 'general antibiotics', unless specifically stated, refers to S01AA, that is, topical ocular antibiotics, excluding sulphonamides and fluoroquinolones. The majority of all drugs included within these drug classes were either not marketed in Scandinavian countries during the study period or were very rarely used.

Individual-level analyses (Denmark)

First, to describe the overall rate of treatment, we calculated the annual incidence rate (IR) of treatment episodes with topical ocular antibiotics, defined as the number of treatment episodes per 1000 children (i.e. per 1000 person-years) per year (2000–2015). Clusters of prescriptions separated by <14 days were considered to belong to the same treatment episode. The analysis was stratified by age at the time of filling the prescription (0–1 years and 2–4 years). To illustrate seasonal variation, we further estimated the monthly IR for the last year in the study period (2015) as well as 2000, 2005 and 2010.

Second, we described the distribution of number of treatment episodes per child by estimating the proportion of all children aged 0–1 years and 2–4 years (defined as age on January 1 in the given year) who received 1, 2 and ≥3 treatment episodes (defined as above) within the given year. Further, for the last year of the study period (2015), we identified children turning 1 through 5 years and identified the number of treatment episodes received in the last 365 days. As an example, for children turning 1 year in 2015, we provided the number of treatment episodes received in the first year of life, and, correspondingly, for children turning 5, the number of treatment episodes received in their fourth year of life.

Lastly, we performed supplementary analyses stratified by region of residency (Region of Southern Denmark, Central Denmark Region, North Denmark Region, Region Zealand, and Capital Region of Denmark) to identify potential regional variation in utilization patterns.

Aggregate data (Scandinavia)

We obtained aggregate data on the annual number of users for topical ocular antibiotics prescribed to children aged 0–4 in Scandinavia for the period from 2000 through 2016. Data from Sweden and Norway were only available from 2004 to 2006, respectively. Using these data, we depicted the annual prevalence (1-year period prevalence) over time in the three countries, that is, the proportion of all children (0–4 years) who received at least one prescription in the given year. Due to the aggregate nature of the data, this analysis had to be performed separately for general antibiotics (ATC, S01AA), sulphonamides (S01AB) and fluoroquinolones (S01AE).

Other

All analyses were performed using STATA 14.2 (StataCorp, College Station, TX, USA). Ethical approval was not required due to the observational nature of the study.

Results

Danish individual-level results

We identified 107 581 Danish children aged 0–4 years who received 271 980

treatment episodes from 2000 through 2015. The average IR of topical ocular antibiotic treatment during the study period was more than twice as high among children aged 0–1 years compared with children aged 2–4 years, with a mean IR per 1000 person-years of 608 compared to 271 (Fig. 1). The annual IR was relatively stable in both age groups up until 2010, where there was an IR of 728 for children aged 0–1 years and 312 for children aged 2–4 years, after which it decreased by 37% for both age groups until 2015 (when compared to 2010, Fig. 1). A marked seasonal variation was seen consistently throughout the study period, with the lowest IRs in July–September (data not shown). Only negligible regional variation was seen when stratifying by the five Danish regions (data not shown).

In 2015, 24% of all Danish children aged 0–1 years received one treatment episode, while 6.1% received two treatment episodes and 1.8% received ≥3 treatment episodes. For children aged 2–4, corresponding numbers were 11%, 1.7% and 0.3%, respectively (Fig. 2). In 2015, the highest proportion of treatment was observed in the second life year, with 42% of the children receiving one or more treatment episodes (Fig. 3). Most children in this age category received one treatment episode (29.1%), 9.6% had two treatment episodes and 3.3% had ≥3 treatment episodes (Fig. 3). Similar results were obtained for previous years (data not shown).

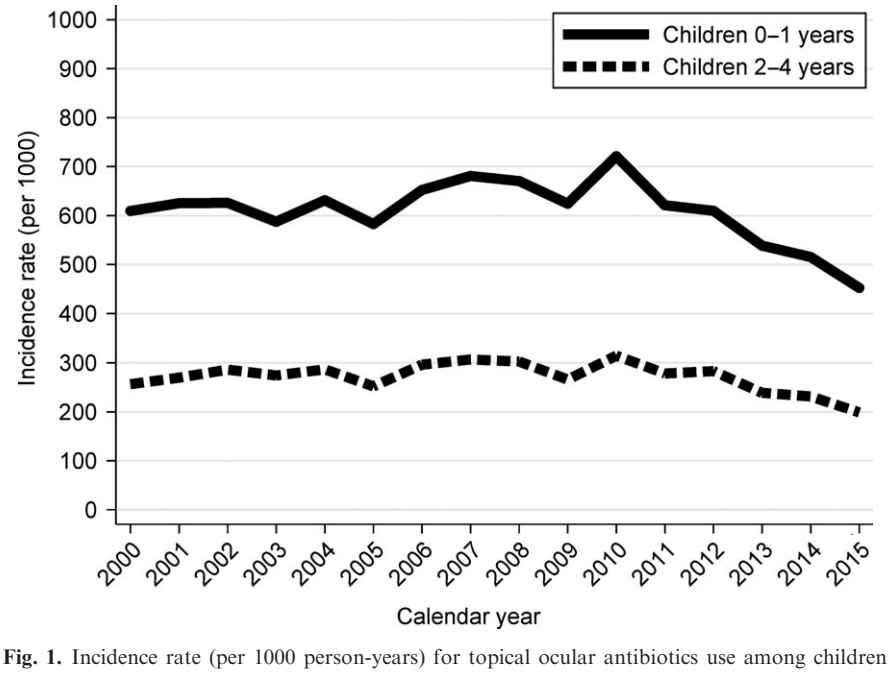

Fig. 1. Incidence rate (per 1000 person-years) for topical ocular antibiotics use among children aged 0–1 years and children aged 2–4 years during 2000–2015 in Denmark.

Scandinavian results

Compared to Norway and Sweden, Denmark had a markedly higher use of general topical ocular antibiotics (Fig. 4) and fluoroquinolones (Table 1), with the latter almost exclusively being used in Denmark. The decrease in use observed in Denmark from 2010 and onwards was also observed in Norway and Sweden (Fig. 4).

The most commonly used single antibiotic substances in the age group 0–4 years in Denmark, Norway and Sweden were chloramphenicol and fusidic acid (selected antibiotics presented in Table 1; the full version is available from the corresponding author upon request). The use of tobramycin increased between 2000 and 2010 in Denmark (from 0 to 52 users per 1000 population), followed by a decrease to 24 per 1000 population in 2016 (Table 1). In 2016, the prescription of tobramycin in Norway (1 of users per 1000 population) and Sweden (0 users per 1000 population) was limited compared with Denmark (24 users per 1000 population; Table 1).

In Denmark, ofloxacin (S01AE01) was the most frequently prescribed fluoroquinolone in 2000–2002 (data not shown), after which ciprofloxacin was more frequently used (Table 1). The prescription rate for fluoroquinolones was much lower in Norway (0–2 users per 1000 children) and Sweden (0–1 users per 1000 children; Table 1). There were no registrations of sulphonamide prescriptions in Norway and Sweden (data not shown). For Danish data, regarding the sulphonamide group (S01AB), the annual number of prescriptions decreased from 1 to 0 during the study period (data not shown).

Discussion

We found a markedly higher use of topical ocular antibiotics in Denmark compared with Norway and, in particular, Sweden. A decrease was seen in the period 2010–2016 in all three countries. Most antibiotics were prescribed to children aged 0–2 years in Denmark. Further, Danish children received prescriptions for fluoroquinolones and tobramycin, which were rarely used in Norway and Sweden.

There are several strengths to this study. The national prescription registry in each Scandinavian country covers all prescriptions in the age group 0–4 years (Wettermark et al. 2013). In Scandinavia, all antibiotics require a prescription from a medical provider and can only be purchased at community pharmacies and are thus captured by the data sources used. While antibiotics can also be dispensed directly from hospitals, the proportion of antibiotics supplied in this way is very small and thus unlikely to have influenced our results (Schmidt et al. 2016). The obtained data include all prescriptions issued by hospitals, general practice and out-of-hours primary care, and filled at community pharmacies. Lastly, the use of fill data ensures that prescriptions issued but never filled do not inflate our results (Pottegård et al. 2014).

A limitation to our study is the lack of information on indications for prescribing topical ocular antibiotics. Conditions where antibiotics for eye infections are prescribed to children include bacterial conjunctivitis, nasolacrimal duct obstruction with purulent discharge and prophylaxis for ophthalmia neonatorum (Wallace & Steinkuller 1998). However, in the paediatric population, keratitis is uncommon (Al-Otaibi 2012; Channa et al. 2016). We thus expect

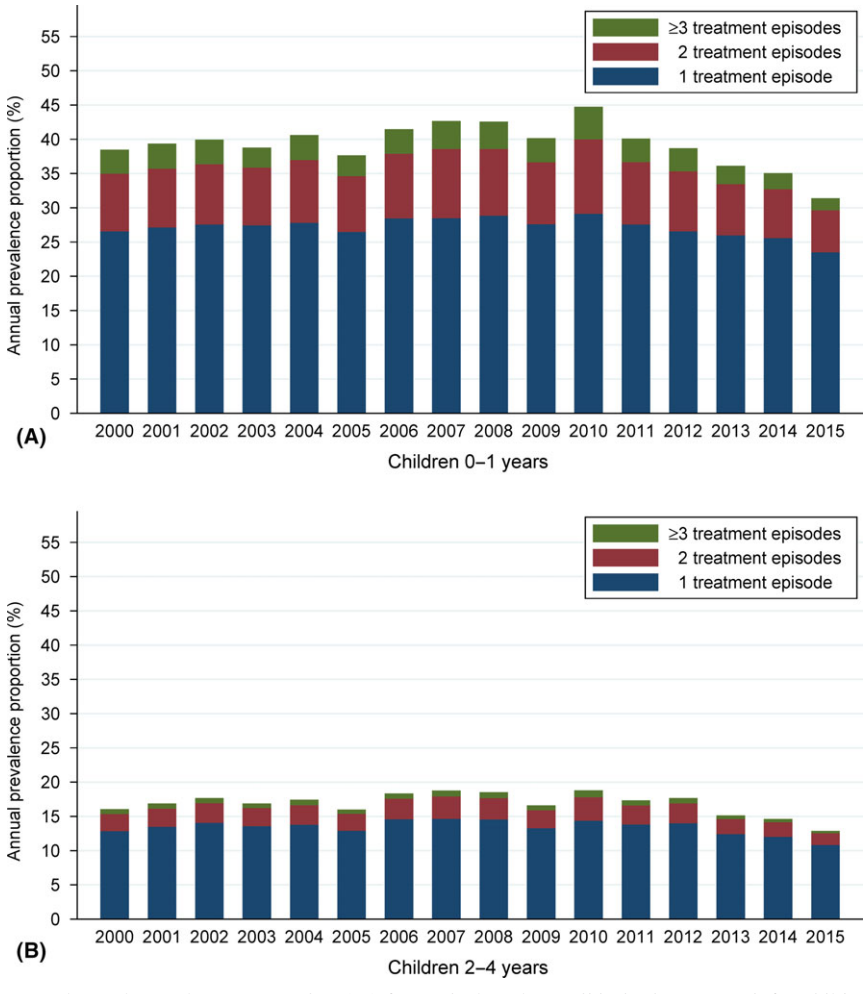

Fig. 2. Annual prevalence proportion (%) for topical ocular antibiotics in Denmark for children aged (A) 0–1 years and (B) 2–4 years in 2000–2015.

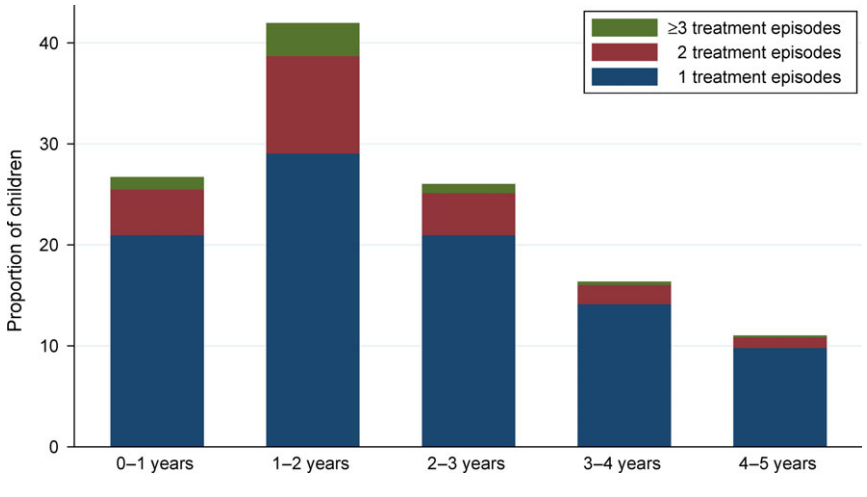

Fig. 3. Proportion of children (%) receiving 1, 2 or ≥3 treatment episodes of topical ocular antibiotics in 2015. Children were categorized in 1-year age categories with a look-back period of 365 from the day of turning 1 year older. As an example, children turning 2 years old in 2015 were included in the second category and their use of topical ocular antibiotics between their first and second birthday was assessed.

topical ocular antibiotics to be prescribed mainly due to conjunctivitis in our study population.

The overwhelming majority of uncomplicated bacterial conjunctivitis cases are self-limiting (Rose et al. 2005; Rietveld et al. 2007; Høvding 2008; Sheikh et al. 2012; Azari & Barney 2013), although antibiotics modestly improve the rate of clinical and microbiological remission (Sheikh et al. 2012). Previous studies in other countries included both children and adults (Rietveld et al. 2007; Shekhawat et al. 2017). Rietveld et al. (2007) found that more than two-thirds of all episodes of infectious conjunctivitis received topical antibiotic treatment, even though only 21% of cases were registered as bacterial conjunctivitis. Children over the age of 11 years and adults accounted for 75% of the participants (Rietveld et al. 2007). According to previous studies, viral conjunctivitis is most common among adults (Azari & Barney 2013), while bacterial conjunctivitis is more common among children (Høvding 2008). Therefore, a lower prescription rate would be expected in the Rietveld study.

The significantly higher antibiotic prescription rate observed in Denmark is of concern, as it may indicate an irrational use of topical ocular antibiotics in Denmark. The differences between the three countries may be explained by differences in the healthcare systems. In Norway and Sweden, a contact to the general practitioner usually requires a small fee (although children are exempt), which may lead to a more restrictive behaviour in seeking medical advice for uncomplicated illnesses. Further, national guidelines are available in both Norway and Denmark. In Denmark, the national guideline promotes rational antibiotic use by recommending a wait-and-see policy in moderate bacterial conjunctivitis, while reserving topical antibiotics for more severe cases (Sundhed.dk 2017). Severe conjunctivitis is defined as excessive lacrimation, redness and oedema both in the conjunctiva and fornices. Only in such cases are children not allowed to return to school or day care before relief of symptoms and treatment with topical antibiotics for at least 2 days (Danish Health Authority 2013). A similar national guideline is present in Norway (The Norwegian Directorate of Health 2016), although specifically promoting the use of delayed prescriptions in mild to moderate cases to relieve symptoms. Both Norwegian and Danish guidelines emphasize that school or day care cannot require parents to seek medical help or initiate topical antibiotics for an eye infection before they reattend. We were

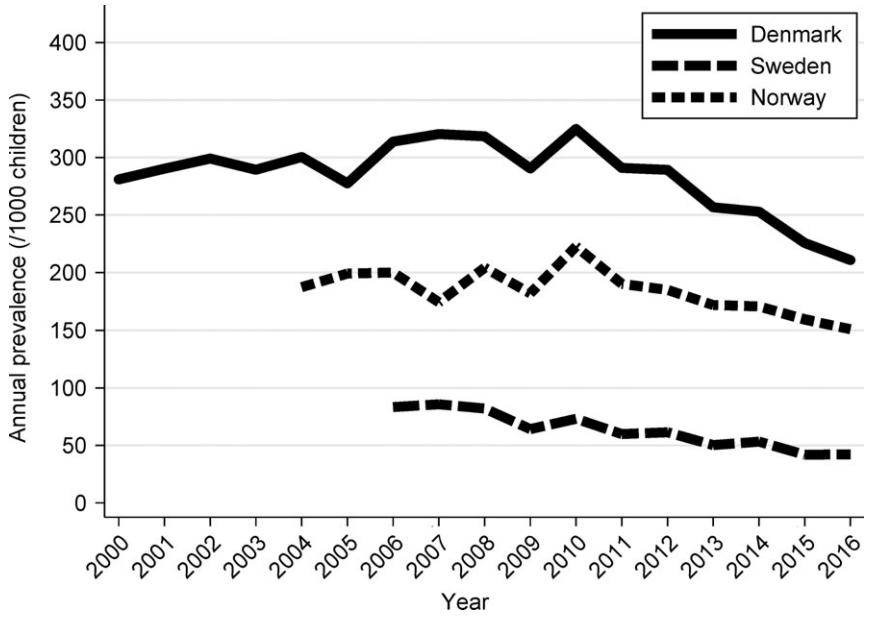

Fig. 4. Annual prevalence proportion of general topical ocular antibiotics (S01AA) in children aged 0–4 years in Denmark, Sweden and Norway.

not able to identify a national guideline for Sweden. A similar treatment guideline is available in the UK, promoting a 2-week delay before seeing a physician in uncomplicated cases (National Health Service 2018).

School and day care policies often dictate that children have to receive antibiotic treatment before being allowed to return, and, consequently, parents might feel a pressure to obtain treatment for their child (Rose et al. 2006). In a recent UK study, 87% of childcare policies excluded children with conjunctivitis and 49% required antibiotic treatment, with 43% of healthcare providers reporting to be influenced by childcare polices when prescribing antibiotics and 15% reporting childcare polices to be the sole reason for prescribing (Finnikin & Jolly 2016). In Denmark, topical ocular antibiotics are often prescribed to children via telephone consultations and during weekends through out-of-hours primary care, that is, without clinical consultations (Huibers et al. 2014). In general practice, infectious conjunctivitis is often seen as 'catch-up consultations', and physicians find it is easier and less time consuming to prescribe antibiotics than to explain the rationale behind declining to prescribe (Rose et al. 2006). Another factor that may contribute to prescribing antibiotics is the difficulty in distinguishing between viral and bacterial conjunctivitis (Everitt & Little 2002; Sheikh et al. 2012; Azari & Barney 2013), with only 36% of general practitioners being certain in their clinical differentiation between the two causes (Everitt & Little 2002). Furthermore, Everitt and Little (2002) found that 95% of general practitioners prescribed topical ocular antibiotics for acute bacterial conjunctivitis despite the suspicion that half of episodes actually were of viral aetiology. As such, general practitioners often prescribe topical ocular antibiotics due to uncertainty of the aetiology of acute conjunctivitis and lack of knowledge about transmission risk and management (Rose et al. 2006). Patients who receive treatment for acute infectious conjunctivitis are often convinced that antibiotics promote faster recovery and are more likely to reattend their physician (Everitt et al. 2006). Compared to the immediate prescribing of topical antibiotics, delayed

Table 1. The total number of users of topical ocular antibiotics per 1000 children aged 0–4 years use in Denmark, Norway and Sweden during 2006 to 2016.

Antibiotic	ATC	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Denmark												
General antibiotics	S01AA	314	320	318	291	325	291	289	257	253	226	211
Chloramphenicol	S01AA01	113	106	98	85	98	80	77	69	70	63	60
Tobramycin	S01AA12	27	38	39	38	52	46	45	37	34	26	24
Fusidic acid	S01AA13	224	231	234	215	239	213	212	188	186	166	153
Fluoroquinolones	S01AE	23	25	24	24	28	28	27	24	19	16	11
Ciprofloxacin	S01AE03	16	18	17	18	21	21	20	17	14	12	11
Norway												
General antibiotics	S01AA	200	174	204	182	223	190	185	172	170	159	151
Chloramphenicol	S01AA01	126	109	128	111	140	121	117	106	110	105	101
Tobramycin	S01AA12	0	1	1	1	1	1	1	1	0	0	1
Fusidic acid	S01AA13	95	81	97	88	109	88	84	75	71	63	57
Fluoroquinolones	S01AE	2	1	0	0	0	0	0	0	0	0	0
Ciprofloxacin	S01AE03	2	1	0	0	0	0	0	0	0	0	0
Sweden												
General antibiotics	S01AA	83	86	82	64	73	60	61	50	53	42	42
Chloramphenicol	S01AA01	41	43	41	31	32	28	19	15	18	16	15
Tobramycin	S01AA12	0	0	0	0	0	0	0	0	0	0	0
Fusidic acid	S01AA13	48	49	47	38	46	36	46	38	38	28	29
Fluoroquinolones	S01AE	1	0	0	0	0	0	0	0	0	0	0
Ciprofloxacin	S01AE03	1	0	0	0	0	0	0	0	0	0	0

ATC = Anatomical therapeutic chemical [10].

prescribing reduced the use of antibiotics by 50%, while also reducing reattendance for eye infections and providing similar symptom control compared with immediate prescribing (Everitt et al. 2006).

The decline in rate of topical ocular antibiotics since 2010 deserves mention. A similar decrease has been seen in Denmark for children's use of oral antibiotics (Reilev et al. 2018). This points towards increasing adherence to the treatment guidelines outlined above. However, a further reduction of the prescription rate of topical ocular antibiotics seems possible, particularly in Denmark. To this end, it could be considered to introduce delayed prescribing for mild to moderate cases of conjunctivitis into the Danish guidelines, similarly as in the Norwegian guidelines. Besides the differences in overall utilization of topical ocular antibiotics between the three countries, the markedly higher use of tobramycin and fluoroquinolones in Denmark is of concern. While the official Danish guidelines do not dictate choice of antibiotic, a commonly used website among healthcare providers (pro.medicin.dk) lists chloramphenicol, fusidic acid and tobramycin as first line treatment, which might explain the higher rate of tobramycin used in Denmark. We have not identified any guidelines recommending fluoroquinolones, and thus this likely comes down to prescribing tradition.

In conclusion, we have documented considerable variation in the utilization of topical ocular antibiotic prescriptions among children aged 0–4 years in Scandinavia, with Denmark having the highest use, followed by Norway and Sweden. Across the Scandinavian countries, however, a decline was noted from 2010 onwards. A coordinated effort in educating parents, day care institutions and health providers seems necessary to promote the rational use of topical ocular antibiotics for acute infectious conjunctivitis in young children.

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