Clinical Epidemiology

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ORIGINAL RESEARCH

Trends in Antibiotic Use in Danish, Finnish, Norwegian and Swedish Children

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Objective: To compare the use of antibiotics in children in four Northern European countries.

Methods: We conducted a register-based study based on individual-level prescription data from national prescription registers. We identified all redeemed outpatient prescriptions for systemic antibiotics in children aged 0–14 years from July 2006 to June 2017 in Denmark, Finland, Norway, and Sweden. We computed incidence rates and incidence rate ratios of treatment episodes with any antibiotic and different antibiotic classes.

Results: In 2016/2017, the rates of antibiotic treatment episodes per 1000 person-years in children aged 0–14 years were 429, 284, 219, and 184 in Finland, Denmark, Sweden, and Norway, respectively, and the rate ratios (95% confidence intervals) compared with Norway were 2.33 (2.33–2.34), 1.54 (1.54–1.55), and 1.19 (1.19–1.20) in Finland, Denmark, and Sweden, respectively. The rate of antibiotic treatment episodes declined over time in all countries. The relative reductions in 2016/2017 compared with 2006/2007 were 36% in Finland, 40% in Denmark, 49% in Sweden, and 29% in Norway. Treatment episodes peaked between age 12 and 18 months. The most used antibiotic class was beta-lactamase sensitive penicillins among all children in Norway and Sweden and among children above two years in Denmark, while penicillins with extended spectrum were most used in Finland and among the youngest children in Denmark.

Conclusion: In all countries, the use of antibiotics in children declined between 2006 and 2017. However, there were still considerable differences in antibiotic use between otherwise quite similar Nordic countries, with a more than 2-fold difference between the countries with the lowest and highest rates. Interventions to reduce the number of antibiotic treatment episodes in the countries with higher rates could reduce the total antibiotic use.

Keywords: antibiotic use, pediatric, multi-national comparison, antimicrobial consumption, prescription patterns

Introduction

In 2015, the World Health Organization launched a Global Action Plan on Antimicrobial Resistance with the objective to increase awareness of antibiotic resistance, prevent infections, optimize the use of antibiotics, increase knowledge through research and surveillance, and foster the development of new antimicrobial drugs.[1] Children are common recipients of antibiotics.[2] Using between-country comparisons of antibiotic prescription rates may reveal areas for promoting rational antibiotic prescribing. In a landmark study, Goossens et al showed that outpatient antibiotic use was markedly lower in Northern than in Southern European countries.[3] Youngster et al recently observed up to seven-fold differences in pediatric antibiotic prescription rates in six countries across Europe, Asia, and North America.[4]

Received: 12 February 2022
Accepted: 30 June 2022
Published: 7 August 2022

The study by Youngster et al used broad age group definitions and varying types of data sources.[4] The Northern European countries Denmark, Finland, Norway, and Sweden have similar tax-funded health care systems and nationwide prescription registers that include antibiotics.[5] Differences in pediatric antibiotic utilization in these countries may therefore help to identify policy differences that could guide interventions to reduce unnecessary antibiotic use.

We undertook a drug-utilization study with the aim to compare the rate of antibiotic treatment episodes among children aged 0–14 years in Denmark, Finland, Norway, and Sweden over time and by age.

Methods

We conducted an observational study using national registers from Denmark, Finland, Norway, and Sweden including information on all children aged 0 years to and including 14 years during the study period 1 July 2006 to 30 June 2017. We selected the study period based on data availability and to describe antibiotic use according to "epidemiological years" as infectious diseases often have a seasonal pattern. We defined an "epidemiological year" as running from 1 July to 30 June.

Setting

The number of children aged 0 to 14 years was lowest in Finland (894,178 in 2016) and highest in Sweden (1,760,994 in 2016; Table S1). Population density is markedly higher in Denmark (143 inhabitants per km^2 in 2016) than in the other countries (14–24 in 2016; Table S1). All countries have governmentally supported daycare available from 6–12 months of age and the proportion of smokers is decreasing in all countries (Table S1). In all four countries, antibiotics require a prescription from a physician and can only be purchased in licensed pharmacies.

Data Sources

We obtained nationwide, individual-level prescription data from the Danish National Prescription Database, the Norwegian Prescription Database, the Swedish Prescribed Drug Register, and the Prescription Register of Finland as well as the Finnish Prescription Centre.[5,6] The Danish, Norwegian, and Swedish prescription registers hold information on all redeemed outpatient prescriptions since 1995, 2004, and 2005, respectively, while the Finnish Prescription Register holds information only on reimbursable redeemed prescriptions since 1994. In Finland, all systemic antibiotics were reimbursable 1994 to 2012, when some reimbursements were withdrawn (Table S2). Collection of all redeemed prescriptions irrespective of reimbursement to the Prescription Centre started gradually in 2010, and in 2017 the register included the majority of prescriptions.[6] We combined data from the two Finnish registers to achieve the most reliable measure of antibiotic use (Figure S1 shows the registrations in each register over the epidemiological years). Antibiotics given to hospitalized or institutionalized patients are not captured by any of the registers,[5] but the registries include information on prescriptions irrespective of provider (private or public).

All the prescription registers include the unique personal identification number, sex, date of redemption, and drug substance classified according to the Anatomical Therapeutic Chemical (ATC) Classification System.[5] Date of birth was obtained from the prescription registers in Finland and Norway (year and month of birth only), and from the Civil Registration System in Denmark,[7] and Statistics Sweden in Sweden. We obtained information on the underlying populations at risk comprising all children aged 0–14 years of age from publicly available national population statistics.[8–11]

Classification of Outcomes

First, we performed analyses for all treatment episodes with antibacterials for systemic use combined (ATC code J01). Antibiotic prescriptions redeemed within 14 days of the previous antibiotic prescription were regarded as one treatment episode. Second, we performed analyses by antibiotic class: tetracyclines (ATC code J01AA), penicillins with extended spectrum (J01CA), beta-lactamase sensitive penicillins (J01CE), other penicillins (J01CF, J01CG, J01CR), other beta-lactam antibacterials (J01D), macrolides, lincosamides and streptogramins (J01F), quinolone antibacterials (J01M), sulfonamides and trimethoprim (J01E), and others (J01B, J01G, J01R, J01X). If a child received prescriptions of different antibiotic classes during one treatment episode, the treatment episode was included in both classes.

Statistical Analysis

We calculated the incidence rates per 1000 person-years of treatment episodes with any antibiotic and different antibiotic classes for both sexes combined and stratified by sex. For each epidemiological year and age group, the corresponding population at risk was used to establish the total amount of follow-up time in person-years.

The combined incidence rate for all children aged 0 to 14 years for each epidemiological year and country was age-standardized with a standard defined by the average number of children in each one-year age group over all countries and epidemiological years. We did not include confidence intervals around rates as the estimates are based on the entire population in each country and thereby avoided uncertainty due to sampling.

We calculated the incidence rate according to age in one-month intervals among children aged up to and including 23 months, and in one-year intervals thereafter. To illustrate the total number of antibiotic treatment episodes from birth to 14 years per child, we estimated the mean number of antibiotic treatment episodes a child would have up to age 15 if it had been subject to the age-specific rates observed in a given epidemiological year (further details in Methods S1).

To compare the incidence between countries we estimated incidence rate ratios and confidence intervals for each epidemiological year using the country with the lowest incidence (Norway) as the reference.[12]

In sensitivity analyses, we repeated the analyses using all redeemed antibiotic prescriptions as the outcome, ie without grouping prescriptions redeemed within 14 days into treatment episodes.

We used Stata version 15.0 (StataCorp, College Station, Texas, USA) and R version 4.0.2.

Results

Throughout the study period, the rates of antibiotic treatment episodes for all children aged 0–14 years were highest in Finland, followed by Denmark, Sweden, and Norway (Figure 1, Table S3). In 2006/2007, the number of antibiotic treatment episodes per child from birth to and including 14 years of age were 10.0, 7.1, 6.5, and 3.9 in Finland, Denmark, Sweden, and Norway, respectively (Table S4). In 2016/2017, the corresponding numbers were 6.4, 4.3, 3.3, and 2.8.

Thus, all countries experienced a decline over the study period although there was a transient increase in 2010/2011 in Denmark and Finland, in 2011/2012 in Norway, and in 2014/2015 in Finland (Figure 1). The relative reductions in 2016/2017 compared with 2006/2007 were 36% in Finland, 40% in Denmark, 49% in Sweden, and 29% in Norway (calculated from Table S3).

Over the years, the relative differences between Norway and the other countries decreased (Figure 2). For Finland the rate ratio compared with Norway was highest in 2010/2011 (2.84; 95%-CI=2.83–2.84) and lowest in 2016/2017 (2.33; 95%-CI=2.33–2.34; Table S5). For Denmark, it was highest in 2010/2011 (1.94; 95%-CI=1.93–1.94) and lowest in 2014/2015 (1.46; 95%-CI=1.45–1.46); for Sweden it was highest in 2006/2007 (1.67; 95%-CI=1.66–1.67) and lowest in 2013/2014 (1.11; 95%-CI=1.10–1.11; Table S5).

Beta-lactamase sensitive penicillins were the most used antibiotics in Denmark, Norway, and Sweden, while penicillins with extended spectrum were most frequently used in Finland (Figure 3). A transient increase in the rate of macrolides was observed in 2010–2012 in Denmark and Finland and in 2011/2012 in Norway and Sweden.

Antibiotic Use According to Age

The rate of antibiotic treatment episodes per 1000 person-years peaked at 12 months of age in Denmark (1377) and Finland (1408), at 15 months in Norway (593), and at 18 months in Sweden (728; Figure 4, Table S6). Thereafter, the rates gradually declined until 12 years of age in all countries, followed by a slight increase. The rates among children below 2 years of age were particularly high in Finland and Denmark, and the higher rates persisted in all ages in Finland in comparison to the other countries (Figure 4). In Denmark, penicillins with extended spectrum were most frequently used until 3 years of age, after which beta-lactamase sensitive penicillins dominated (Figure 5). In Finland, penicillins with extended spectrum were consistently the most used antibiotic class across all ages, while beta-lactamase sensitive penicillins were most frequent in Norway and Sweden across all ages.

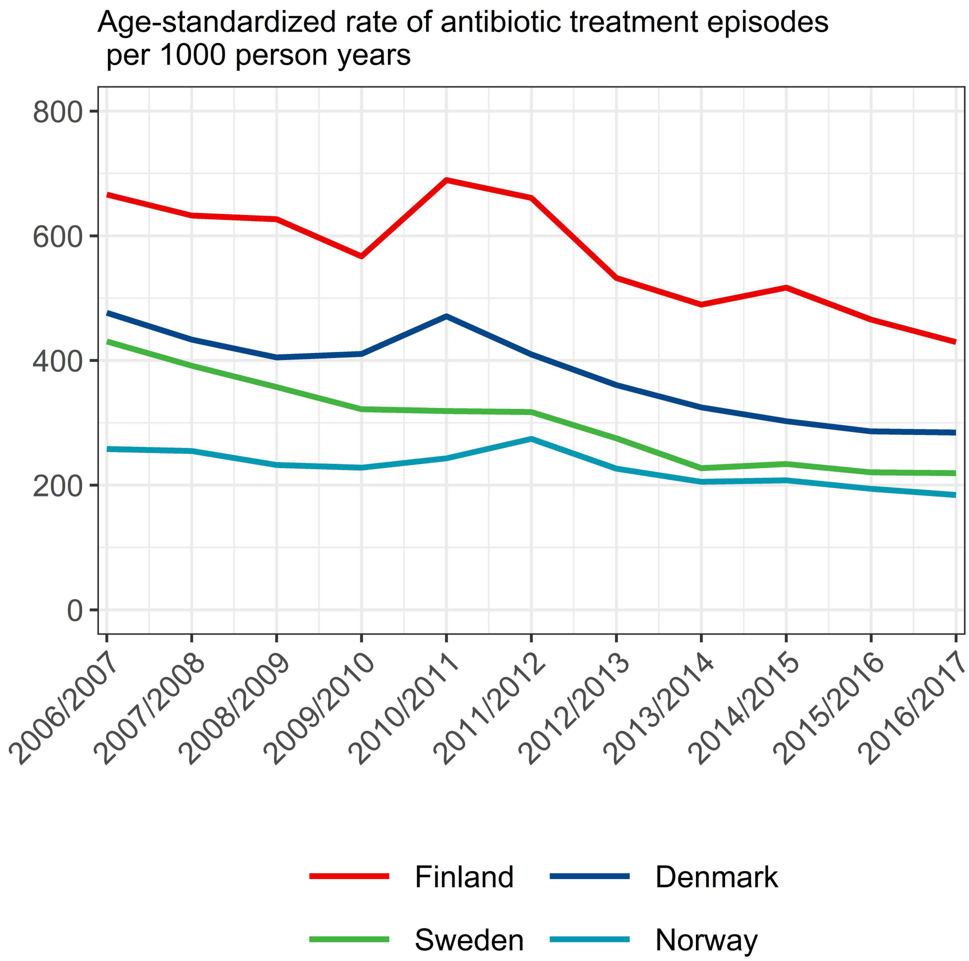

Figure 1 Age-standardized incidence rates of treatment episodes with systemic antibiotics (ATC J01) among children aged 0–14 years by epidemiological years.

Antibiotic Use According to Sex

The rate of antibiotic treatment episodes was consistently higher for boys than girls in Finland with the reverse seen in Norway (Figure S2; Table S4). However, the sex differences varied by antibiotic class (Figure S3). Starting from birth, the rates were higher among boys than girls in all countries and for most subclasses; in Denmark, Norway, and Sweden, the rate for girls surpassed that of boys after 3–5 years of age, while in Finland, the rates for girls and boys were very similar after 4 years of age (Figure 4 and Figure S4).

Sensitivity Analyses

Results were similar when all antibiotic prescriptions were considered, although the rates were considerably higher than for antibiotic treatment episodes (Figure S5 and S6 and Table S7 and S8).

Discussion

Based on nationwide data on redeemed antibiotic prescriptions issued to children aged 0–14 years in outpatient care during 2006/2007–2016/2017, we found that while the rate decreased in all countries over the study period, there were considerable differences in the rate of antibiotic treatment episodes, with the highest rates in Finland, followed by Denmark, Sweden, and Norway. In all countries, the rates were highest in young children, but the peak was higher and occurred considerably earlier in Denmark and Finland. Penicillins with extended spectrum were the most frequently used

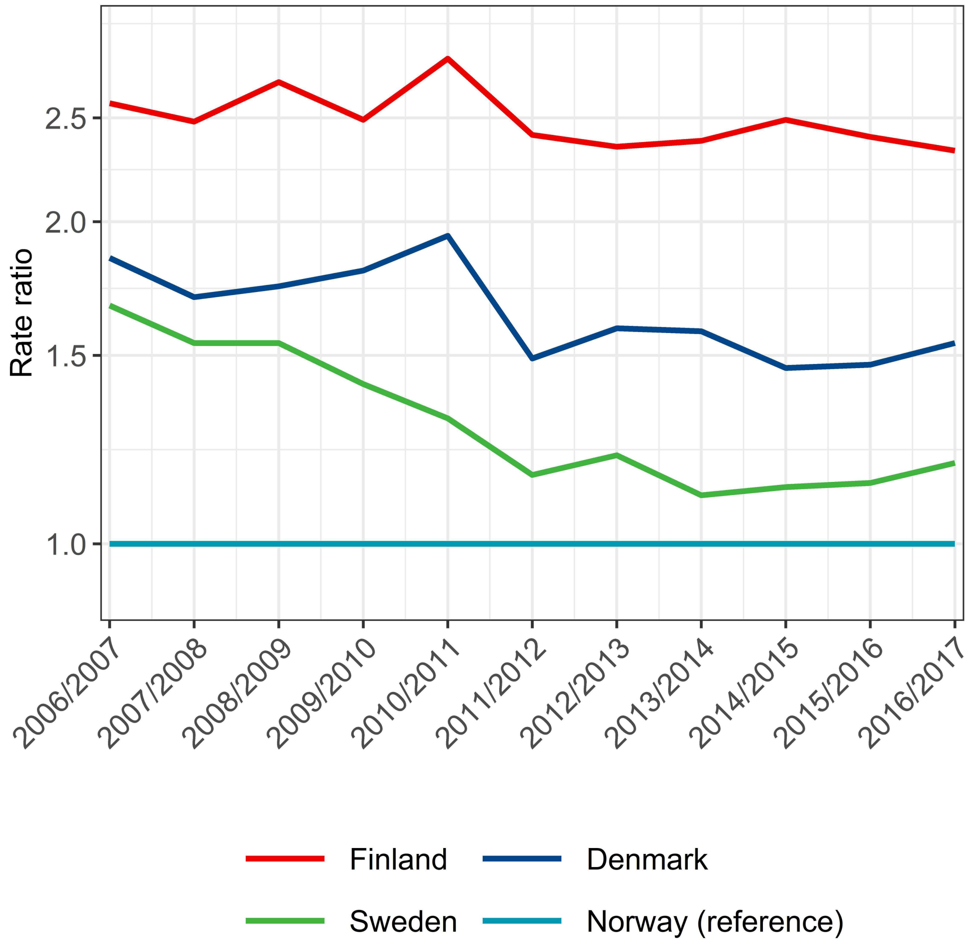

Figure 2 Rate ratios between countries in the age standardized incidence rates of treatment episodes with systemic antibiotics (ATC J01) among children aged 0–14 years by epidemiological year.

antibiotics in Finland at all ages and among the youngest children in Denmark, while beta-lactamase sensitive penicillins were most frequently used in Norway and Sweden.

The present study is based on unique nationwide prescription registers that allowed comparison of antibiotic use according to age, sex, and different antibiotic classes among children across four similar countries over a ten-year period. A limitation is that the prescription registers do not capture antibiotics provided at hospitals, although prescriptions written at hospitals and redeemed at pharmacies are included.[5,13] It is likely that numbers of antibiotic prescriptions were underestimated in 2012 to 2016 in Finland, because some antibiotics targeted to the youngest children (mixtures of sulfa-trimethoprim, cephalexin, and phenoxymethylpenicillin) were no longer reimbursable and thus not included in the Finnish Prescription Register. However, the Finnish Prescription Centre, which include all prescriptions irrespective of reimbursement, received partial reporting during 2012 to 2016 and reporting has been mandatory since 2017, giving quite reliable estimates for the epidemiological year 2016/2017.[6] In line with our findings, other European countries have also observed declines in pediatric antibiotic use over recent years.[14–16]

The absolute rates and trends in antibiotic use observed in the current study must be interpreted in light of the relatively low absolute rates in the Nordic countries compared with other countries. For example, for persons below 20 years in the USA, there were 790 antibiotic prescriptions per 1000 persons in 2016.[17] Also, for all age groups, the 2016 European Centre for Disease Prevention and Control data shows that the defined daily doses of antibiotics per 1000 inhabitants were 25 in Spain, 24 in France, and 17 in the United Kingdom compared with 15 in Denmark, Norway, and Finland and 12 in Sweden.[18] The overall declines observed in this study align with findings from older single-country

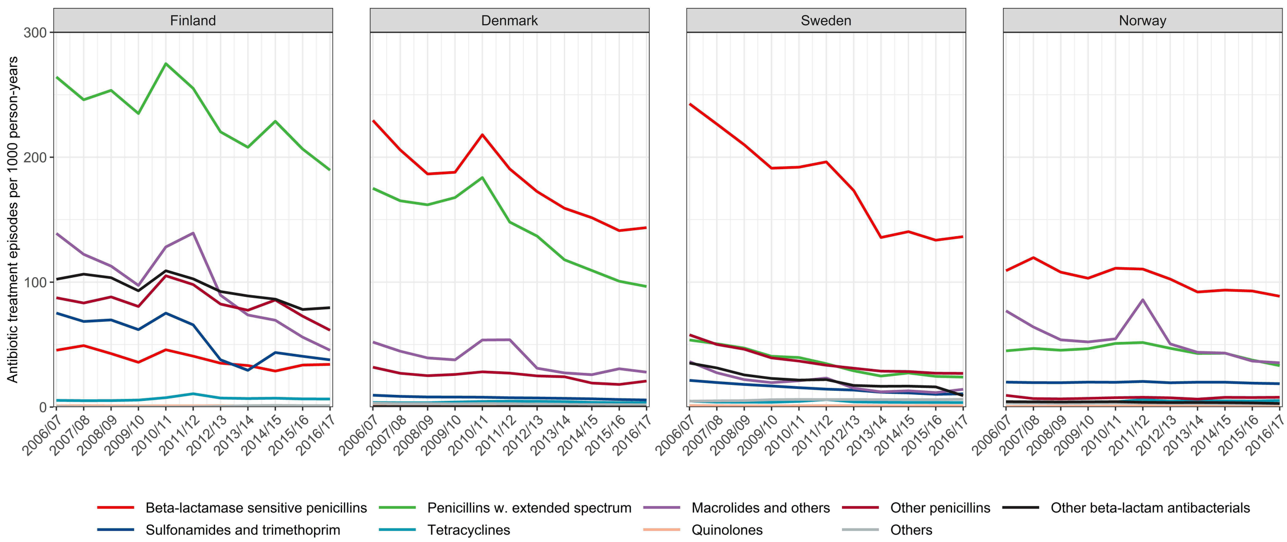

Figure 3 Age-standardized incidence rates of treatment episodes with different classes of systemic antibiotics (ATC J01) among children aged 0–14 years by epidemiological year in Finland, Denmark, Sweden, and Norway.
Note: The reimbursement change in Finland effect the episodes of sulfonamides and trimethoprim, other beta-lactam antibacterials and beta-lactamase sensitive penicillins.

studies from Denmark,[13,19] Finland,[20] and Sweden.[21,22] We extend these findings by comparing rates across four similar, Nordic countries, applying the same methodology, which ensured comparability.

Many factors likely contribute to the between-country differences and the differences over time within each country in the use of pediatric antibiotics. Below we describe some of the factors that might contribute to the differences.

The observed transient increase in prescription rates during 2010/2012 is most likely explained by *Mycoplasma pneumoniae* epidemics,[20,23–25] also indicated by the increased use of macrolides during this period. However, we also observed an increase in treatment episodes with other antibiotics in Denmark and Finland, while this was not the case in Norway, indicating more restrictive prescription practices in Norway.

Any policy leading to lower transmission of respiratory infections is likely to reduce antibiotic use, as observed during the COVID-19 pandemic.[26] We have no information indicating changes in behavioral policies to reduce transmission of infection during the study period. However, the pneumococcal conjugate vaccine (PCV) was introduced in a three-dose infant schedule in 2006 in Norway, 2007 in Denmark, gradually from 2007 in Sweden, and in 2010 in Finland (Table S1).This could have contributed to the decline in the rate of antibiotic use, as PCV vaccination programs have previously been shown to reduce antibiotic use.[27] Furthermore, declines in adult smoking over the years (Table S1) might also explain some of the decline in the antibiotic use, as environmental smoking is associated with higher risk of respiratory infections.[28]

The use of antibiotics was highest during the first two years of life in all Nordic countries, in alignment with previous reports.[13,20] However, our results indicate great variation within these first years of life. In the first months of life, we found limited use of outpatient antibiotics, which could, in part, be due to protection against infections by maternal antibodies and breastfeeding.[29] Sweden had the highest peak age in the rate of antibiotic treatment episodes (18 months), which may be related to longer parental leaves (68 weeks) and potentially older average age when starting daycare (Table S1). Until 18 months of age, boys had a higher use of antibiotics than girls, which may be related to young boys being more susceptible to some infectious diseases than girls.[30]

Increased awareness of antimicrobial resistance and the importance of restrictive antibiotic prescribing policies have likely contributed to the declining use of antibiotics. However, despite the similar trends, we found considerable differences between the countries. The differences may be explained by variations in timing and content of country-specific initiatives aiming to restrict antibiotic prescribing. The importance of adopting a surveillance system with an integrated approach, tracking annual antimicrobial usage and resistance, is well-recognized.[31]

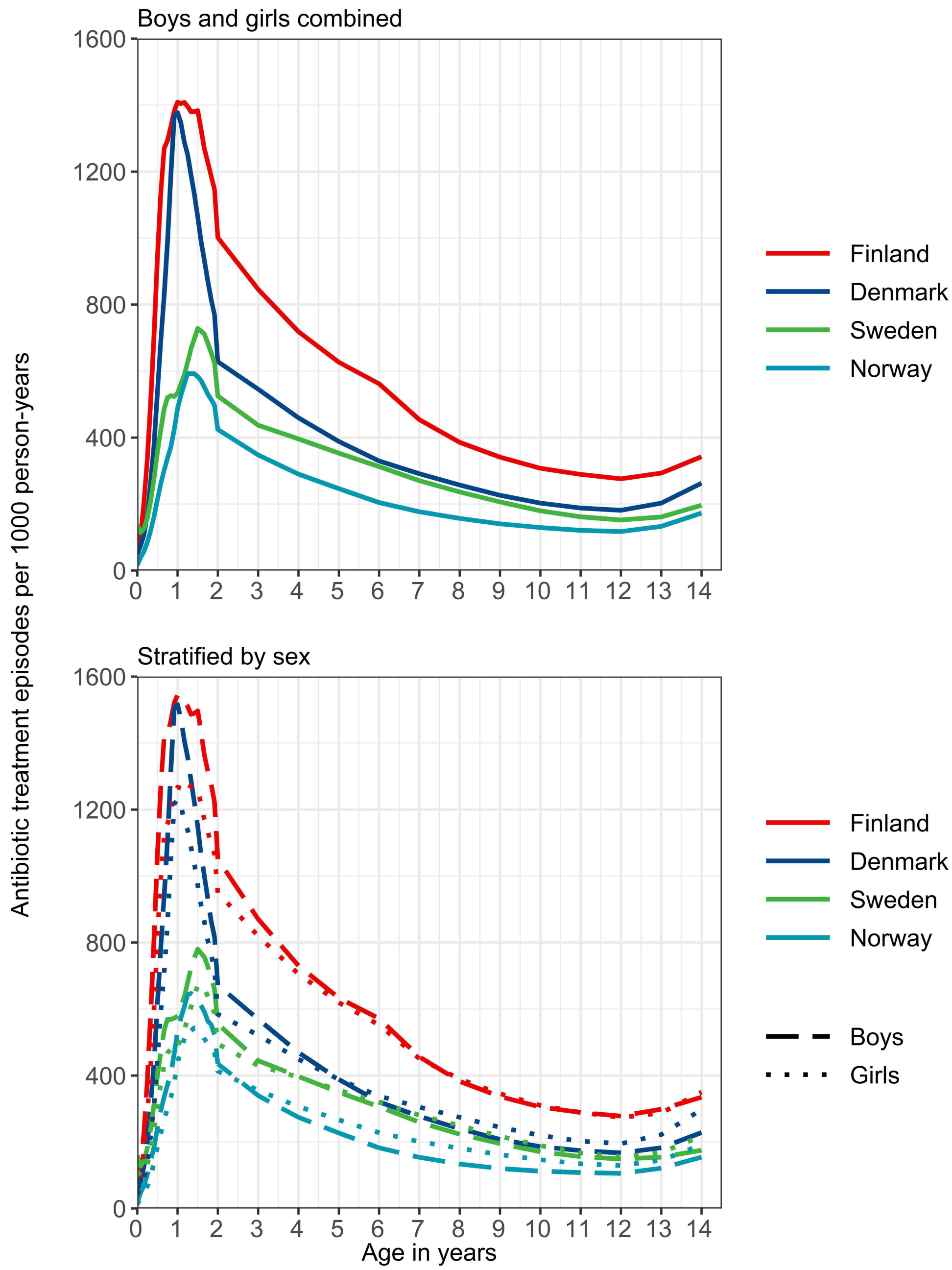

Figure 4 Incidence rates of treatment episodes with systemic antibiotics (ATC J01) by age got boys and girls combined and stratified by sex.
Note: Rates are estimated in one-month intervals among children aged up to and including 23 months and in one-year intervals thereafter.

Such comprehensive surveillance systems have been implemented in Denmark (1995),[32] Norway (2000),[33] and Sweden (2002),[34] while Finland has had fragmented reporting in these areas.[35,36] Explicit targets for reductions in human antibiotic use were first set in 2009 in Sweden,[37] in 2015 in Norway,[33] and in 2017 in Denmark[38] and Finland.[39] However, other initiatives were taken; for instance, Finland launched the first cross-administrative recommendation on the control of antimicrobial resistance and the development of antimicrobial policies in 2000.[40]

All Nordic countries have tax-supported health care systems, but a survey from 2013/2014 showed that 52% of Finnish children were also covered by supplemental health insurances, facilitating easier access to private care providers.[41] This may in part explain the high antibiotic use in Finland as private providers may be more willing to prescribe antibiotics to secure patient satisfaction.[42,43]

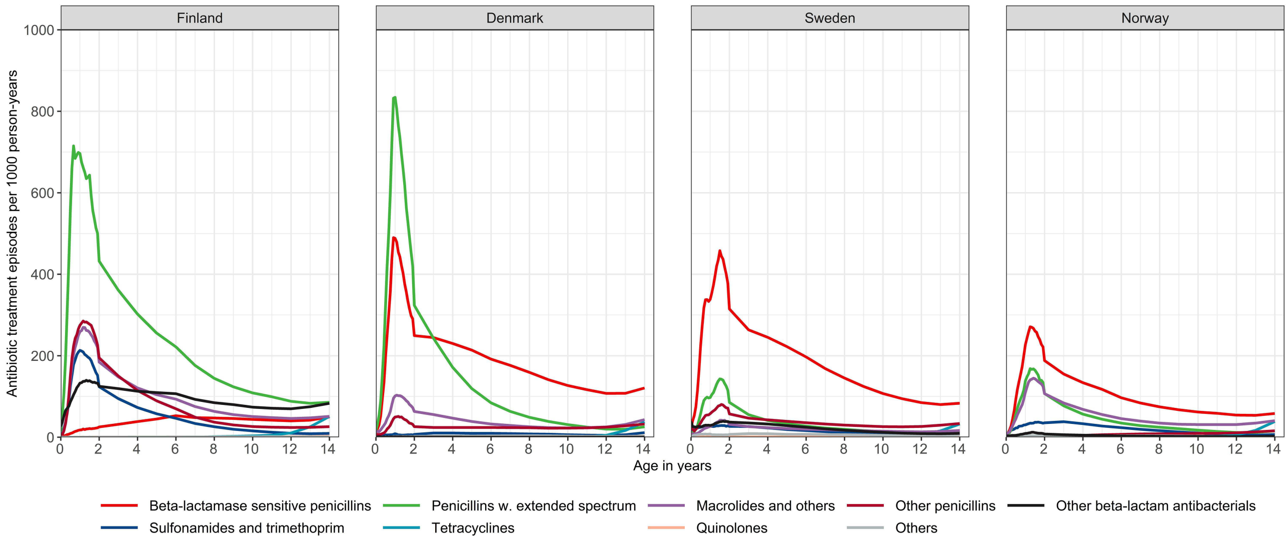

Figure 5 Incidence rates of treatment episodes with different classes of systemic antibiotics by age in Finland, Denmark, Sweden, and Norway.
Note: Rates are estimated in one-month intervals among children aged up to and including 23 months and in one-year intervals thereafter.

It has previously been found that antibiotic prescription rates and classes of antibiotics vary between different settings, which might be attributed to different guidelines and habits of prescriptions.[44] The high use of penicillins with extended spectrum in Finland is related to guidelines recommending amoxicillin (a penicillin with extended spectrum) as the first-line therapy for the treatment of otitis media.[45] Conversely, phenoxymethylpenicillin (a beta-lactamase sensitive penicillin) is recommended as first-line therapy for most respiratory tract infections (including otitis media) in Denmark, Norway and Sweden.[46–48] Thus, the relatively high use of penicillins with extended spectrum in Denmark is inconsistent with guidelines. This discrepancy has previously been attributed to the preferred taste of amoxicillin mixture over phenoxymethylpenicillin, particularly among the youngest children.[49] However, in Sweden and Norway beta-lactamase sensitive penicillins are used most frequently also among the youngest children.

Conclusion

The rate of pediatric antibiotic use from 2006/2007 to 2016/2017 showed a general decline in all countries. Although all countries had quite low rates in an international perspective, there were still differences in pediatric antibiotic use between countries. Norway had the lowest antibiotic use during the study period, followed by Sweden, Denmark and Finland. The present study cannot directly associate the differences in pediatric antibiotic use between the countries and the differences in each country over time to specific explanatory factors. However, factors contributing to the pediatric use of antibiotics may include the underlying infectious disease pressure as exemplified by the increased use during *Mycoplasma pneumoniae* epidemics, infectious disease preventive measures like introduction of the PCV vaccine, lifestyle factors like parental smoking, society structures like length of parental leave and use of private health care providers, the surveillance on antibiotic use and resistance, and overall initiatives to reduce unnecessary antibiotic prescribing.

In all countries, antibiotic use was highest in the first years of life. Therefore, interventions in this age group could potentially have a large impact on antibiotic use. Based on the data from Norway, it could be possible to significantly reduce and even more than half the use of antibiotics in other Nordic countries.

Transparency Statement

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

Data Sharing Statement

Data on antibiotic prescriptions used in this study arises from nationwide registers. Due to data protection rules, we are not allowed to share the individual-level data, but other researchers fulfilling the requirements from the data providers could obtain similar data.

Ethical Approval

Ethical approval is not required for registry-based studies in Denmark. The study was approved by the Danish Data Protection Agency. In Finland, the study was approved by the Institutional Review Board of the Finnish Institute for Health and Welfare and the data processing permissions were obtained from the respective register controllers. In Norway and Sweden, respectively, study approval was obtained from the Regional Ethics Committee, South-East Norway and the Regional Ethical Review Board, Stockholm, Sweden.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was funded by NordForsk (grant number: 83839). The funder had no role in considering the study design or in the collection, analysis, or interpretation of data, writing of the report, or the decision to submit the article for publication.

Disclosure

The authors report no relation that could be construed as a conflict of interest. AAP and HN are investigators in vaccine-related studies for which THL has received funding from GSK, Pfizer and Sanofi Pasteur. AAP reports grants from Nordforsk, during the conduct of the study.

References

1. World Health Organization. *Global Action Plan on Antimicrobial Resistance*. Geneva, Switzerland: World Health Organization; 2015.
2. Clavenna A, Bonati M. Drug prescriptions to outpatient children: a review of the literature. *Eur J Clin Pharmacol*. 2009;65:749–755. doi:10.1007/s00228-009-0679-7
3. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet*. 2005;365:579–587. doi:10.1016/S0140-6736(05)17907-0
4. Youngster I, Avorn J, Belleudi V, et al. Antibiotic use in children - a cross-national analysis of 6 countries. *J Pediatr*. 2017;182:239–44 e1. doi:10.1016/j.jpeds.2016.11.027
5. Wettermark B, Zoega H, Furu K, et al. The Nordic prescription databases as a resource for pharmacoepidemiological research–a literature review. *Pharmacoepidemiol Drug Saf*. 2013;22:691–699. doi:10.1002/pds.3457
6. Aarnio E, Huupponen R, Martikainen JE, Korhonen MJ. First insight to the Finnish nationwide electronic prescription database as a data source for pharmacoepidemiology research. *Res Social Adm Pharm*. 2020;16:553–559. doi:10.1016/j.sapharm.2019.06.012
7. Schmidt M, Pedersen L, Sorensen HT. The Danish civil registration system as a tool in epidemiology. *Eur J Epidemiol*. 2014;29:541–549. doi:10.1007/s10654-014-9930-3
8. StatBank Denmark. FOLK3: population 1. Statistics Denmark; 2019. Available from: https://www.statbank.dk/statbank5a/default.asp?w=1920. Accessed october 20, 2019.
9. Population according to age (1-year) and sex, 1970-2018. Statistics Finland, 2019. Available from: http://pxnet2.stat.fi/PXWeb/pxweb/en/StatFin/StatFin__vrm__vaerak/statfin_vaerak_pxt_11rd.px/?rxid=a1086bbe-667f-485d-9eaf-4c61ac4e07df. Accessed october 20, 2019.
10. Population by region, marital status, age and sex. Year 1968-2018. Statistics Sweden, 2019. Available from: http://www.statistikdatabasen.scb.se/pxweb/en/ssd/START__BE__BE0101__BE0101A/BefolkningNy/?rxid=f5bf3beb.). Accessed October 20, 2019.
11. Statistics Norway. Population, by sex and one-year age groups (M) 1986-2019. Statistics Norway; 2019. Available from: https://www.ssb.no/en/statbank/table/07459/. Accessed October 20, 2019.
12. Kumar M. dsr: compute directly standardized rates, ratios and Differences; 2019.
13. Pottegard 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:e16–22. doi:10.1097/INF.0000000000000519

14. Neilly MDJ, Guthrie B, Hernandez santiago V, Vadiveloo T, Donnan PT, Marwick CA. Has primary care antimicrobial use really been increasing? Comparison of changes in different prescribing measures for a complete geographic population 1995–2014. *J Antimicrob Chemother*. 2017;72:2921–2930. doi:10.1093/jac/dkx220
15. Gradl G, Teichert M, Kieble M, Werning J, Schulz M. Comparing outpatient oral antibiotic use in Germany and the Netherlands from 2012 to 2016. *Pharmacoepidemiol Drug Saf*. 2018;27:1344–1355. doi:10.1002/pds.4643
16. Holstiege J, Schulz M, Akmatov MK, Steffen A, Batzing 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. doi:10.2807/1560-7917.ES.2020.25.31.1900599
17. Centers for Disease Control and Prevention. Outpatient antibiotic prescriptions. United States, 2016. Available from: https://www.cdc.gov/antibiotic-use/data/report-2016.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fantibiotic-use%2Fcommunity%2Fprograms-measurement%2Fstate-local-activities%2Foutpatient-antibiotic-prescriptions-US-2016.html. Accessed May 17, 2021.
18. Country overview of antimicrobial consumption. European centre for disease prevention and control; 2021. Availabe from: https://www.ecdc.europa.eu/en/antimicrobial-consumption/database/country-overview. Accessed May 17, 2021.
19. Reilev M, Thomsen RW, Aabenhus R, Sydenham RV, Hansen JG, Pottegard A. Switching between antibiotics among Danish children 0-4 years of age: a nationwide drug utilization study. *Pediatr Infect Dis J*. 2018;37:1112–1117. doi:10.1097/INF.0000000000001961
20. Parviainen S, Saastamoinen L, Lauhio A, Sepponen K. Outpatient antibacterial use and costs in children and adolescents: a nationwide register-based study in Finland, 2008–16. *J Antimicrob Chemother*. 2019;74:2426–2433. doi:10.1093/jac/dkz208
21. Tyrstrup M, Beckman A, Molstad S, et al. Reduction in antibiotic prescribing for respiratory tract infections in Swedish primary care-a retrospective study of electronic patient records. *BMC Infect Dis*. 2016;16:709. doi:10.1186/s12879-016-2018-9
22. Hogberg L, Oke T, Geli P, Lundborg CS, Cars O, Ekdahl K. Reduction in outpatient antibiotic sales for pre-school children: interrupted time series analysis of weekly antibiotic sales data in Sweden 1992–2002. *J Antimicrob Chemother*. 2005;56:208–215. doi:10.1093/jac/dki147
23. Uldum SA, Bangsborg JM, Gahrn-Hansen B, et al. Epidemic of Mycoplasma pneumoniae infection in Denmark, 2010 and 2011. *Euro Surveill*. 2012;17:20073.
24. Blix HS, Vestrheim DF, Hjellvik V, Skaare D, Christensen A, Steinbakk M. Antibiotic prescriptions and cycles of Mycoplasma pneumoniae infections in Norway: can a nationwide prescription register be used for surveillance? *Epidemiol Infect*. 2015;143:1884–1892. doi:10.1017/S0950268814002908
25. Linde A, Ternhag A, Torner A, Claesson B. Antibiotic prescriptions and laboratory-confirmed cases of Mycoplasma pneumoniae during the epidemic in Sweden in 2011. *Euro Surveill*. 2012;17. doi:10.2807/ese.17.06.20082-en
26. van de Pol AC, Boeijen JA, Venekamp RP, et al. Impact of the COVID-19 pandemic on antibiotic prescribing for common infections in the Netherlands: a primary care-based observational cohort study. *Antibiotics*. 2021;10:196. doi:10.3390/antibiotics10020196
27. Palmu AA, Rinta-Kokko H, Nohynek H, Nuorti JP, Jokinen J. Impact of national ten-valent pneumococcal conjugate vaccine program on reducing antimicrobial use and tympanostomy tube placements in Finland. *Pediatr Infect Dis J*. 2018;37:97–102. doi:10.1097/INF.0000000000001810
28. Vanker A, Gie RP, Zar HJ. The association between environmental tobacco smoke exposure and childhood respiratory disease: a review. *Expert Rev Respir Med*. 2017;11:661–673. doi:10.1080/17476348.2017.1338949
29. Niewiesk S. Maternal antibodies: clinical significance, mechanism of interference with immune responses, and possible vaccination strategies. *Front Immunol*. 2014;5:446. doi:10.3389/fimmu.2014.00446
30. Muenchhoff M, Goulder PJ. Sex differences in pediatric infectious diseases. *J Infect Dis*. 2014;209(Suppl 3):S120–6. doi:10.1093/infdis/jiu232
31. Anderson M, Clift C, Schulze K, et al. *Averting the AMR Crisis: What are the Avenues for Policy Action for Countries in Europe? Health Systems and Policy Analysis: Policy Brief*. Copenhagen, Denmark: World Health Organization. Regional Office for Europe, European Observatory on Health Systems and Policies; 2019.
32. DANMAP 2017. *Use of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria from Food Animals, Food and Humans in Denmark*. Copenhagen, Denmark; 2018:1600–2032.
33. NORM/NORM-VET 2018. *Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway*. Tromsø/Oslo,Norway; 2019:1502–2307.
34. Swedres-Svarm 2019. *Sales of Antibiotics and Occurrence of Resistance in Sweden*. Solna/ Uppsala,Sweden; 2020:1650–6332.
35. Finres 1997–2010. *Antimicrobial Resistance in Finland*. ISBN: 978-952-302-062-7. Tampere, Finland; 2013.
36. FINRES-Vet reports. Finnish food authority; 2018. Available from: https://www.ruokavirasto.fi/en/farmers/animal-husbandry/animal-medication/monitoring-of-antibiotic-resistance/finres-vet-reports/. Accessed September 9, 2020.
37. Molstad S, Lofmark S, Carlin K, et al. Lessons learnt during 20 years of the Swedish strategic programme against antibiotic resistance. *Bull World Health Organ*. 2017;95:764–773. doi:10.2471/BLT.16.184374
38. World Health Oraganization. *National Action Plan on Antibiotics in Human Healthcare*. Copenhagen, Denmark: Danish Ministry of Health; 2017.
39. Hakanen A, Jalava J, Kaartinen L. *The National Action Plan on Antimicrobial Resistance 2017–2021*. Helsinki, Finland: Ministry of Social Affairs and Health; 2017.
40. World Health Oraganization. *Fighting Bacterial Resistance to Antibiotics and Developing Antibiotic Policies*. Helsinki, Finland: Finnish Ministry of Social Affairs and Health; 2000.
41. Valtonen H, Kempers J, Karttunen A. *Supplementary Health Insurance in Finland -Consumer Preferences and Behaviour*. Helsinki, Finland: Kela Research Department; 2014.
42. Zgierska A, Rabago D, Miller MM. Impact of patient satisfaction ratings on physicians and clinical care. *Patient Prefer Adherence*. 2014;8:437–446. doi:10.2147/PPA.S59077
43. Granlund D, Zykova YV. Can private provision of primary care contribute to the spread of antibiotic resistance? A study of antibiotic prescription in Sweden. *Pharmacoecon Open*. 2021;5:187–195. doi:10.1007/s41669-020-00234-7
44. Butler CC, Hood K, Verheij T, et al. Variation in antibiotic prescribing and its impact on recovery in patients with acute cough in primary care: prospective study in 13 countries. *BMJ*. 2009;338:b2242. doi:10.1136/bmj.b2242
45. Current Care Summary: Acute otitis media. The Finnish medical society duodecim; 2017. Available from: https://www.kaypahoito.fi/en/ccs00071. Accessed July 23, 2021.

46. Clinical guidelines for general practice. Respiratory tract infections - diagnosis and treatment. Danish Society for General Practice; 2014. Available from: https://vejledninger.dsam.dk/luftvejsinfektioner/. Accessed July 23, 2021.
47. Use of antibiotics in primary health care. Infections in children. Norwegian Directorate of Health; 2020. Available from: https://www.antibiotikaiallmennpraksis.no/index.php?action=showtopic&topic=vjdQuFdN&j=1. Accessed July 23, 2021.
48. Folkhälsomyndigheten. Treatment recommendations for common infections in outpatient care; 2021. Available from: https://www.folkhalsomyndigheten.se/publicerat-material/publikationsarkiv/b/behandlingsrekommendationer-for-vanliga-infektioner-i-oppenvard/. Accessed May 17, 2022.
49. Pottegard A, Hallas J. [Children prefer bottled amoxicillin]. *Ugeskr Laeger*. 2010;172:3468–3470. Danish.