Switching Between Antibiotics Among Danish Children 0-4 Years of Age
A Nationwide Drug Utilization Study

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Introduction

Antibiotics are the most frequently prescribed drugs in children, with more than half of children ≤1 year having received at least one antibiotic prescription. However, antibiotics are often prescribed for common non-bacterial conditions which is of some concern, as inappropriate use of antibiotics contributes to the selection and spread of antibiotic-resistant bacteria as well as disrupting the individual-level endogenous microbiota. The most common indication for antibiotic treatment among children is upper and lower respiratory tract infections, with beta-lactamase sensitive penicillin (phenoxymethylpenicillin) being the first-line treatment in the community according to Danish antibiotic guidelines. In spite of this, amoxicillin – a penicillin with extended spectrum – has previously been prescribed to a similar extent as phenoxymethylpenicillin among children younger than 4 years in Denmark. The reason for this apparent discrepancy is not fully understood. One hypothesis is that the poor taste of oral suspensions containing phenoxymethylpenicillin is an important reason for parents and physicians to choose amoxicillin in small children, either as initial treatment or as second-line therapy after initial and unsuccessful treatment attempts with phenoxymethylpenicillin. Data on initial versus second-line use and switching between different types of antibiotics in children are, however, scarce.

In a previous paper, we provided a thorough description of the overall utilization of antibiotics among Danish children aged ≤4 years from 2000 to 2012. In this paper, we extend this description by evaluating the annual incidence of episodes treated with antibiotics, the choice of initial antibiotic treatment and switching patterns between different types of antibiotics among children aged ≤4 years from 2000 to 2015.
Materials and methods

In this nationwide, descriptive drug utilization study, we investigated antibiotic use and trends in switching between antibiotics among children aged 0-4 years from 2000 to 2015.

Ethics

This study was approved by the Danish Data Protection Agency (jr.2015-57-0008). According to Danish legislation, studies based solely on register data do neither require approval from an ethics committee nor informed consent from individuals in the study population.12

Data sources

Data were retrieved from the National Prescription Registry which records individual-level information on prescribed medication dispensed from community pharmacies to Danish residents since 1995.13 Among other variables, each record includes the substance, the date of purchase and a unique person identifier. The indication for prescribing is generally not available. Drugs are classified according to WHO’s anatomical-therapeutic-chemical (ATC) system.14 In Denmark, all antibiotics require a prescription from a medical provider and can only be purchased at monopolized community pharmacies. As such, nationwide information on all oral antibiotics prescribed in an outpatient setting is available.

Population

We identified all children in the Danish National Prescription Registry, who were ≤4 years at the time of filling a prescription of oral antibiotics (ATC J01) from January 1, 2000 to December 31, 2015. Study subjects were further required to be permanent residents in Denmark from birth until inclusion in the study. Among children fulfilling these criteria, we extracted all prescriptions of antibiotics (ATC J01) and mapped treatment episodes over time. Clusters of prescriptions separated by less than 14 days were considered to belong to the same treatment episode.
Analysis

First, we estimated the annual incidence of treatment episodes with antibiotics, defined as number of treatment episodes per 1000 children in the population per year. The total number of children younger than 4 years of age in Denmark on January the 1st in the specific year was used as the denominator. Additionally, we described the distribution of initially prescribed antibiotics (phenoxymethylpenicillin, amoxicillin, amoxicillin with enzyme inhibitor, ampicillin, macrolides, dicloxacinilin and others) in all incident treatment episodes per year.

Second, we estimated the cumulative risk of switching to another antibiotic within the same treatment episode (i.e. 14 days from the first prescription fill). The analysis was done regarding all treatment episodes and by restricting to the first treatment episode for each child. Switching occurring within day 1-3 was *a priori* defined as an early switch, which might be attributed to taste or other reasons for early non-adherence (including adverse events), while switching within day 4-14 was defined as late switch, more likely attributed to treatment failure or adverse events.

Third, we described the overall variations in the initial choice of antibiotics (penicillin, amoxicillin and other types of antibiotics) from one treatment episode to another, by describing the initially prescribed antibiotic for each of the first 5 separate treatment episodes of each child (censoring children upon turning 5 years).

All analyses were stratified by age groups (0-1 years; 2-4 years) at first treatment episode and by region of residency (Region of Southern Denmark, Central Denmark Region, North Denmark Region, Region Zealand and Capital Region of Denmark).

If prescriptions of two or more antibiotics were filled on the same date, the order of fillings could not be determined. To this end, 0.7% (n=24,926) treatment episodes were excluded in all analyses of choice of initial treatment and of switching patterns.
Other

All analyses were performed using STATA 14.2 (StataCorp, College Station, TX, USA).

Results

We identified 998,852 children aged 0-4 years, filling 4,298,812 prescriptions for antibiotics from 2000-2015, in 3,481,684 unique treatment episodes. Of all children included, 23% filled one prescription, 43% filled 2-4 prescriptions, while 34% filled five or more prescriptions between age 0 and 4.

Annual incidence rate and distribution of initial choice of antibiotics

The annual incidence rate of episodes treated with antibiotics (Figure 1) was consistently higher among children aged 0-1 years compared to children aged 2-4 years. In general, we observed a stable annual incidence rate both among children aged 0-1 years (approx. 880 per 1000) and among children aged 2-4 years (approx. 610 per 1000) from 2000 until 2011. Hereafter, a pronounced decrease was observed in both age groups throughout the remainder of the study period (to 559 per 1000 and 364 per 1000 children in 2015, respectively) (Figure 1). Some variations in annual incidence rates were seen across the five Danish regions (Supplementary figure 1).

With an overall use of 39% and 44%, respectively, phenoxymethylpenicillin and amoxicillin were the most frequently prescribed antibiotics as initial treatment within the study period (Figure 2). The recommended first-line agent, phenoxymethylpenicillin, was the most frequent initial choice in 2000 (46% vs. 37% amoxicillin). However, amoxicillin as initial treatment increased over time and exceeded phenoxymethylpenicillin as the most frequent initial choice of antibiotic from 2005 to 2015, during which amoxicillin constituted 44-51% of initial treatment, compared to 37-44% for phenoxymethylpenicillin (Figure 2). We found similar results when stratifying by age groups, though the relative use of amoxicillin was higher among the youngest children (Supplementary figure 2).

Cumulative risk of switching within treatment episodes
Among children who initially filled a prescription of phenoxymethylpenicillin, 4.7% \((n=85,666)\) had an early switch, most commonly to amoxicillin \((64\%, \ n=54,445)\). Among those who initially filled a prescription of amoxicillin, the risk of early switching was lower \((1.0\%, \ n= 5,399)\) with 39% switching to macrolides (Figure 3). These results did not change during the study period or when restricting the analysis to the first treatment episode for each child (data not shown). When stratifying by age groups, children aged 0-1 years were more likely to switch than older children and this difference between age groups was more pronounced when switching from phenoxymethylpenicillin (Supplementary figure 3).

Variations in initially prescribed antibiotics in subsequent treatment episodes

When evaluating overall variations in initially prescribed antibiotics in subsequent treatment episodes, we found that approximately 40% of those who received phenoxymethylpenicillin as initial treatment in one treatment episode also received phenoxymethylpenicillin as initial antibiotic in the subsequent treatment episode (Figure 4). When restricting to children aged 0-1 years (i.e., censoring upon turning two), the proportion of users of phenoxymethylpenicillin in two subsequent treatment episodes declined to 25% (Supplementary figure 4). The proportion of consistent users was slightly higher (approximately 45%) among children who received amoxicillin as initial treatment in two subsequent treatment episodes (Figure 4).
Discussion

In this nationwide 16-year drug utilization study, we described the use and switching of antibiotics among children aged 0-4 years. Overall, we found a pronounced decrease in the overall annual incidence of antibiotic use from 2011 and onwards. Further, amoxicillin had become the most frequent initial choice of antibiotic since 2005. In general, the risk of early switching was low, though considerably higher among those who received phenoxymethylpenicillin as initial treatment compared to amoxicillin.

Strengths and limitations of this study

The major strength of this study is the use of the Danish Health Registries, covering the entire Danish population regardless of socio-economic and demographic characteristics. In Denmark, antibiotics are not available over the counter. As such we identified all individual-level antibiotic use in the primary health care sector prescribed for home use by any privately practising specialists such as general practitioners, ear, nose and throat physicians and paediatricians, and by specialist physicians in hospital-based, outpatient clinics. Further, our data represent antibiotics that have actually been bought at the pharmacy rather than antibiotic prescriptions, eliminating bias from primary non-adherence. All together, the use of these data sources thereby allows a truly nationwide assessment of antibiotic use over time.

An important limitation of the study is the lack of information about early discontinuation. Only those switching to another antibiotic are captured in this study, leaving us without information on those who discontinue treatment without switching. Similarly, we do not have information about the underlying indication for prescribing an antibiotic, as this has not been systematically recorded in the Danish National Prescription registry until recently. Further, information on allergy, non-compliance, treatment failure and laboratory test results, such as use of microbiological diagnostics or C-reactive protein testing, to support the diagnosis or justify the choice of treatment are not available on a
nationwide level. To this end, it was impossible to determine whether the choice of initial antibiotic or switching to a specific second-line antibiotic was appropriate. It is, however, highly unlikely that the availability of such information would justify the extensive use of amoxicillin as initial treatment observed in this study. Importantly, the vast majority of all infections among young children in primary care is constituted by respiratory tract infections\(^{17}\) for which phenoxymethylpenicillin has been the recommended first-line antibiotic during the entire study period\(^7\). Non-adherence to antibiotic guidelines has been demonstrated in other European countries.\(^{3,18,19}\) However, the extensive use of amoxicillin likely indicates a substantial degree of non-adherence in Denmark as well, despite Denmark being known for its restrictive use of antibiotics.\(^{20}\)

*Comparison with existing literature*

The overall utilization of antibiotics varies considerably across countries in Europe, Asia and North America with the highest rates in Asia and Southern Europe.\(^{21}\) The use in Denmark is among the lowest in Europe.\(^4,20\) Compared to other European countries, the use of beta-lactamase sensitive penicillin among children is high in Denmark (approximately 40%), compared to around 5-15% in Germany, the UK and the Netherlands.\(^{17,22,23}\) This pronounced difference in usage is presumably due to differences in guidelines and traditions across these countries. Despite a theoretically improved antibacterial coverage of amoxicillin compared to phenoxymethylpenicillin, improved clinical outcomes associated with first-line use of amoxicillin have, to the best of our knowledge, not been demonstrated. Even though the increased risk of amoxicillin-resistant streptococci in respiratory tract infections may be short lived,\(^{24}\) the effect of widespread use of amoxicillin on Gram negative bacteria remains a concern.

The pronounced decline in the overall annual incidence of treatment episodes among children from 2011 and onwards corresponds well to previously published Danish data.\(^{5,25}\) The reason behind this is likely multifactorial. First, several initiatives have been taken by the Danish Health Authorities within
the recent years to reduce the use of antibiotics, including new guidelines\textsuperscript{7,26,27} and campaigns targeting health care professionals and patients\textsuperscript{28}. Further, the introduction of an update on the pneumococcal conjugate vaccine (PCV-13) in 2010 may have caused a further decrease in serious pneumococcal infections\textsuperscript{29} although the impact on community respiratory tract infections overall is more uncertain.\textsuperscript{30} Finally, both the overall use of microbiological point-of-care tests as well as antibiotic prescriptions preceded by a microbiological point-of-care test has increased markedly within the study period, possibly supporting a more appropriate use of antibiotics.\textsuperscript{31}

Though the overall risk of switching between antibiotics was low in this study, our results does show that switching from phenoxyemethylpenicillin to amoxicillin is more common than the opposite. Especially among the youngest, a possible cause of early switching within day 1-3 is non-compliance caused by the preferred palatability of amoxicillin compared to phenoxyemethylpenicillin.\textsuperscript{9,10,11} This may have an impact on the decision to switch between antibiotics shortly after initiating therapy as well as on the preference to prescribe amoxicillin as initial therapy. Early adverse events may similarly affect switching patterns and initial choice of therapy.

\textit{Conclusions}

The annual incidence of episodes treated with antibiotics among Danish children aged 0-4 years has decreased considerably since 2011. In contrast to guideline recommendations, amoxicillin is the most frequently used initial treatment. Early switching between antibiotics is uncommon. Initiatives should address the extensive use of amoxicillin.
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Figures

**Figure 1.** Incidence rate of antibiotic treatment episodes (per 1000 person-years) of all antibiotics among Danish children aged 0-4 years, stratified on age groups.
Figure 2. The distribution of the most frequently used antibiotics among Danish children aged 0-4 years over time.
**Figure 3.** The cumulative risk of switching to a new antibiotic when using phenoxyethylpenicillin or amoxicillin, respectively, as initial treatment, among Danish children aged 0-4 years during 2000-2015.
Figure 4. Riverplot illustrating variations in the initial choice of antibiotics in the first 5 subsequent treatment episodes among Danish children aged 0-4 during 2000-2015. The size of the nodes represents the proportion of users within each category i.e., phenoxymethylpenicillin (green), amoxicillin (blue) and any other antibiotics (red). The thickness of the links between categories illustrates the size of the flow, i.e. the proportion of users of phenoxyemethylpenicillin, amoxicillin or any other antibiotics who had a subsequent treatment episode with either phenoxyemethylpenicillin, amoxicillin or any other antibiotics. The difference in volume between links and nodes represents the number of children who did not fill additional prescriptions of antibiotics before the end of their fourth year.
Supplementary material.

Legends:

**Supplementary figure 1.** Incidence rate of antibiotic treatment episodes (per 1000 person-years) of all antibiotics among Danish children aged 0-4 years, stratified by region.
Supplementary figure 2. The distribution of the most frequently used antibiotics among Danish children aged 0-1 years (1A) and children aged 2-4 years of age (1B).

A)

B)
Supplementary figure 3.

The cumulative risk of switching to a new antibiotic when using phenoxymenthylpenicillin or amoxicillin, respectively, as initial treatment, among Danish children during 2000-2015, stratified by age groups.
**Supplementary figure 4.** Riverplot illustrating variations in the initial choice of antibiotics in the first 5 subsequent treatment episodes, restricted to Danish children younger than 2 years during 2000-2015. The size of the nodes represents the proportion of users within each category i.e., phenoxymerphylpenicillin (green), amoxicillin (blue) and any other antibiotics (red). The thickness of the links between categories illustrates the size of the flow, i.e. the proportion of users of phenoxymerphylpenicillin, amoxicillin or any other antibiotics who had a subsequent treatment episode with either phenoxymerphylpenicillin, amoxicillin or any other antibiotics. The difference in volume between links and nodes represents the number of children who did not fill additional prescriptions of antibiotics before the end of their second year.