The Pediatric Infectious Disease Journal Publish Ahead of Print

DOI: 10.1097/INF.0000000000001961

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

Mette Reilev, MD[1], Reimar W. Thomsen, MD, PhD[2], Rune Aabenhus, MD[3], Rikke V. Sydenham, MD[1], Jens Georg Hansen, MD, DMSc[4], and Anton Pottegård, MSc Pharm, PhD[5]

1. The Research Unit of General Practice, Department of Public Health, University of Southern Denmark, DK-5000 Odense, Denmark
2. Department of Clinical Epidemiology, Aarhus University Hospital, DK-8200 Aarhus N, Denmark
3. Section of General Practice and Research Unit for General Practice, Department of Public Health, University of Copenhagen, DK-1014 Copenhagen, Denmark
4. Specialist in general medicine
5. Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, DK-5000 Odense, Denmark

Corresponding author: Mette Reilev, Clinical Pharmacology and Pharmacy, University of Southern Denmark, J.B. Winsløws Vej 19, 2, DK-5000 Odense C, Denmark. E-mail: mreilev@health.sdu.dk, Tlf: +45 8173 8024

Abbreviated Title: Switching Between Antibiotics Among Danish Children

Running Head: Switching Between Antibiotics Among Children

Supports: None

Funding: None

Disclosures: Mette Reilev, Reimar W Thomsen, Rune Aabenhus, Rikke V Sydenham, Jens Georg Hansen, Anton Pottegård: no conflicts of interest or funding to disclose**.**

Acknowledgement

Martin Thomsen Ernst (University of Southern Denmark) is acknowledged for assistance with data management. No compensation was provided for this contribution.

Financial disclosure

Mette Reilev, Reimar W Thomsen, Rune Aabenhus, Rikke V Sydenham, Jens Georg Hansen, Anton Pottegård: none to declare**.**

Abstract

Background: In Denmark, the use of amoxicillin is widespread among children, despite phenoxymethylpenicillin being recommended as first-line therapy. The reason for this apparent discrepancy is not fully understood. We aimed at evaluating prescribing patterns of antibiotics among Danish children aged 0-4 years, with emphasis on incidence of treatment episodes, choice of initial antibiotic treatment and switching patterns between different types of antibiotics.

Methods: We identified all children ≤4 years who filled a prescription of antibiotics from 2000-2015 according to the nationwide Danish National Prescription Registry. We estimated the incidence rate of episodes treated with antibiotics and the choice of initial antibiotic treatment over time. Further, we assessed the cumulative risk of switching within 0-3 days after initiating therapy.

Results: We identified 3,481,684 antibiotic treatment episodes issued to 0-4 year-olds from 2000-2015. The incidence rate was stable until 2011 both among children aged 0-1 years (approx. 880 per 1000) and among children aged 2-4 years (approx. 610 per 1000), after which it dropped. Phenoxymethylpenicillin and, increasingly, amoxicillin were most frequently used as initial treatments (39% vs. 44%). Few switched from amoxicillin (1%) or phenoxymethylpenicillin (4.7%) within the first three days. Of those who switched from phenoxymethylpenicillin, 64% received amoxicillin as second-line treatment.

Conclusion: The 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.

Keywords: Antibiotics, switching, children, drug utilization

Introduction

Antibiotics are the most frequently prescribed drugs in children,[1] with more than half of children ≤1 year having received at least one antibiotic prescription.[2] However, antibiotics are often prescribed for common non-bacterial conditions[3] 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.[4,5] The most common indication for antibiotic treatment among children is upper and lower respiratory tract infections,[6] with beta-lactamase sensitive penicillin (phenoxymethylpenicillin) being the first-line treatment in the community according to Danish antibiotic guidelines.[7] 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.[8] The reason for this apparent discrepancy is not fully understood. One hypothesis is that the poor taste of oral suspensions containing phenoxymethylpenicillin[9,10] is an important reason for parents and physicians to choose amoxicillin in small children,[11] 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 ≤4 years of age from 2000 to 2012.[8] 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 ≤4 years of age 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 0-4 years of age 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, dicloxacillin 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 0-4 years of age, 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 0-1 years of age compared with children 2-4 years of age. In general, we observed a stable annual incidence rate both among children 0-1 years of age (approx. 880 per 1000) and among children 2-4 years of age (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 (Fig., **Supplemental Digital Content 1, http://links.lww.com/INF/D17**).

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 (Fig., **Supplemental Digital Content 2, http://links.lww.com/INF/D18**).

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 0-1 years of age were more likely to switch than older children and this difference between age groups was more pronounced when switching from phenoxymethylpenicillin (Fig., **Supplemental Digital Content 3, http://links.lww.com/INF/D19**).

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 0-1 years of age (i.e., censoring upon turning two), the proportion of users of phenoxymethylpenicillin in two subsequent treatment episodes declined to 25% (Fig., **Supplemental Digital Content 4, http://links.lww.com/INF/D20**). 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 0-4 years of age. 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.[15] Further, our data represent antibiotics that have actually been bought at the pharmacy rather than antibiotic prescriptions, eliminating bias from primary non-adherence.[16] 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[7,26,27] and campaigns targeting health care professionals and patients[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[29] although the impact on community respiratory tract infections overall is more uncertain.[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.[31]

Though the overall risk of switching between antibiotics was low in this study, our results does show that switching from phenoxymethylpenicillin 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 phenoxymethylpenicillin.[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.

Conclusions

The annual incidence of episodes treated with antibiotics among Danish children 0-4 years of age 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.

References

1. Clavenna, A. & Bonati, M. Drug prescriptions to outpatient children: a review of the literature. *Eur. J. Clin. Pharmacol.* **65,** 749–755 (2009).
2. Jensen, J. N., Bjerrum, L., Boel, J., Jarløv, J. O. & Arpi, M. Parents' socioeconomic factors related to high antibiotic prescribing in primary health care among children aged 0-6 years in the Capital Region of Denmark. *Scand. J. Prim. Health Care* **34,** 274–281 (2016).
3. Ivanovska, V. *et al.* Antibiotic prescribing for children in primary care and adherence to treatment guidelines. *J. Antimicrob. Chemother.* **71,** 1707–1714 (2016).
4. Goossens, H., Ferech, M., Vander Stichele, R. & Elseviers, M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *The Lancet* **365,** 579–587 (2005).
5. The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme. *DANMAP 2015 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark*. (Statens Serum Institut, 2015).
6. Vaz, L. E. *et al.* Recent Trends in Outpatient Antibiotic Use in Children. *PEDIATRICS* **133,** 375–385 (2014).
7. Danish Pharmaceutical Information. [Guide for use of antibiotics] (in Danish). Available at: http://pro.medicin.dk/Specielleemner/Emner/318019. (Accessed: 16th November 2016)
8. Pottegård, A. *et al.* Use of antibiotics in children: a Danish nationwide drug utilization study. *Pediatr. Infect. Dis. J.* **34,** e16-22 (2015).
9. Steele, R. W. *et al.* A double-blind taste comparison of pediatric antibiotic suspensions. *Clin. Pediatr. (Phila.)* **36,** 193–199 (1997).

10. Baguley, D., Lim, E., Bevan, A., Pallet, A. & Faust, S. N. Prescribing for children – taste and palatability affect adherence to antibiotics: a review. *Arch. Dis. Child.* **97,** 293–297 (2012).
11. Pottegård, A. & Hallas, J. [Children prefer bottled amoxicillin]. *Ugeskr. Laeger* **172,** 3468–3470 (2010).
12. Thygesen, L. C., Daasnes, C., Thaulow, I. & Bronnum-Hansen, H. Introduction to Danish (nationwide) registers on health and social issues: Structure, access, legislation, and archiving. *Scand. J. Public Health* **39,** 12–16 (2011).
13. Pottegård, A. *et al.* Data Resource Profile: The Danish National Prescription Registry. *Int. J. Epidemiol.* (2016). doi:10.1093/ije/dyw213
14. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2017. (2017).
15. Schmidt, M., Hallas, J., Laursen, M. & Friis, S. Data Resource Profile: Danish online drug use statistics (MEDSTAT). *Int. J. Epidemiol.* **45,** 1401–1402g (2016).
16. Pottegård, A. *et al.* Primary non-adherence in general practice: a Danish register study. *Eur. J. Clin. Pharmacol.* **70,** 757–763 (2014).
17. Dekker, A. R. J., Verheij, T. J. M. & van der Velden, A. W. Antibiotic management of children with infectious diseases in Dutch Primary Care. *Fam. Pract.* cmw125 (2017). doi:10.1093/fampra/cmw125
18. Malo, S. *et al.* Compliance with recommendations on outpatient antibiotic prescribing for respiratory tract infections: the case of Spain. *Basic Clin. Pharmacol. Toxicol.* **116,** 337–342 (2015).

19. Dekker, A. R. J., Verheij, T. J. M. & van der Velden, A. W. Inappropriate antibiotic prescription for respiratory tract indications: most prominent in adult patients. *Fam. Pract.* **32,** 401–407 (2015).
20. Holstiege, J. *et al.* Systemic antibiotic prescribing to paediatric outpatients in 5 European countries: a population-based cohort study. *BMC Pediatr.* **14,** 174 (2014).
21. Youngster, I. *et al.* Antibiotic Use in Children - A Cross-National Analysis of 6 Countries. *J. Pediatr.* **182,** 239–244.e1 (2017).
22. Holstiege, J. & Garbe, E. Systemic antibiotic use among children and adolescents in Germany: a population-based study. *Eur. J. Pediatr.* **172,** 787–795 (2013).
23. Schneider-Lindner, V., Quach, C., Hanley, J. A. & Suissa, S. Secular trends of antibacterial prescribing in UK paediatric primary care. *J. Antimicrob. Chemother.* **66,** 424–433 (2011).
24. Malhotra-Kumar, S. *et al.* Impact of amoxicillin therapy on resistance selection in patients with community-acquired lower respiratory tract infections: a randomized, placebo-controlled study. *J. Antimicrob. Chemother.* **71,** 3258–3267 (2016).
25. Aabenhus, R., Siersma, V., Hansen, M. P. & Bjerrum, L. Antibiotic prescribing in Danish general practice 2004–13. *J. Antimicrob. Chemother.* **71,** 2286–2294 (2016).
26. Danish Ministry of Health: *[Guide for use of antibiotics] (in Danish)*. (2012).
27. Danish College of General Practitioners. *[Guide for respiratory tract infections - diagnosis and treatment] (in Danish)*. (2014).
28. Danish Ministry of Health: [Antibiotics of not?] (in Danish). Available at: http://www.antibiotikaellerej.dk/. (Accessed: 1st February 2017)

29. Harboe, Z. B. *et al.* Impact of 13-valent pneumococcal conjugate vaccination in invasive pneumococcal disease incidence and mortality. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **59,** 1066–1073 (2014).

30. Groth, C., Thomsen, R. W. & Ovesen, T. Association of pneumococcal conjugate vaccination with rates of ventilation tube insertion in Denmark: population-based register study. *BMJ Open* **5,** e007151 (2015).

31. Haldrup, S. *et al.* Microbiological point of care testing before antibiotic prescribing in primary care: considerable variations between practices. *BMC Fam. Pract.* **18,** (2017).

Figures

Figure 1. Incidence rate of antibiotic treatment episodes (per 1000 person-years) of all antibiotics among Danish children 0-4 years of age, stratified on age groups.

Figure 2. The distribution of the most frequently used antibiotics among Danish children 0-4 years of age over time.

Figure 3. The cumulative risk of switching to a new antibiotic when using phenoxymethylpenicillin or amoxicillin, respectively, as initial treatment, among Danish children 0-4 years of age during 2000-2015.

Figure 4. Riverplot illustrating variations in the initial choice of antibiotics in the first 5 subsequent treatment episodes among Danish children 0-4 years of age 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 phenoxymethylpenicillin, amoxicillin or any other antibiotics who had a subsequent treatment episode with either phenoxymethylpenicillin, 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.

Supplemental Digital Content Legends:

Supplemental Digital Content 1. Incidence rate of antibiotic treatment episodes (per 1000 person-years) of all antibiotics among Danish children 0-4 years of age, stratified by region.

Supplemental Digital Content 2. The distribution of the most frequently used antibiotics among Danish children 0-1 years (1A) and children 2-4 years of age (1B).

Supplemental Digital Content 3.

The cumulative risk of switching to a new antibiotic when using phenoxymethylpenicillin or amoxicillin, respectively, as initial treatment, among Danish children during 2000-2015, stratified by age groups.

Supplemental Digital Content 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., 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 phenoxymethylpenicillin, amoxicillin or any other antibiotics who had a subsequent treatment episode with either phenoxymethylpenicillin, 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.

Figure 1

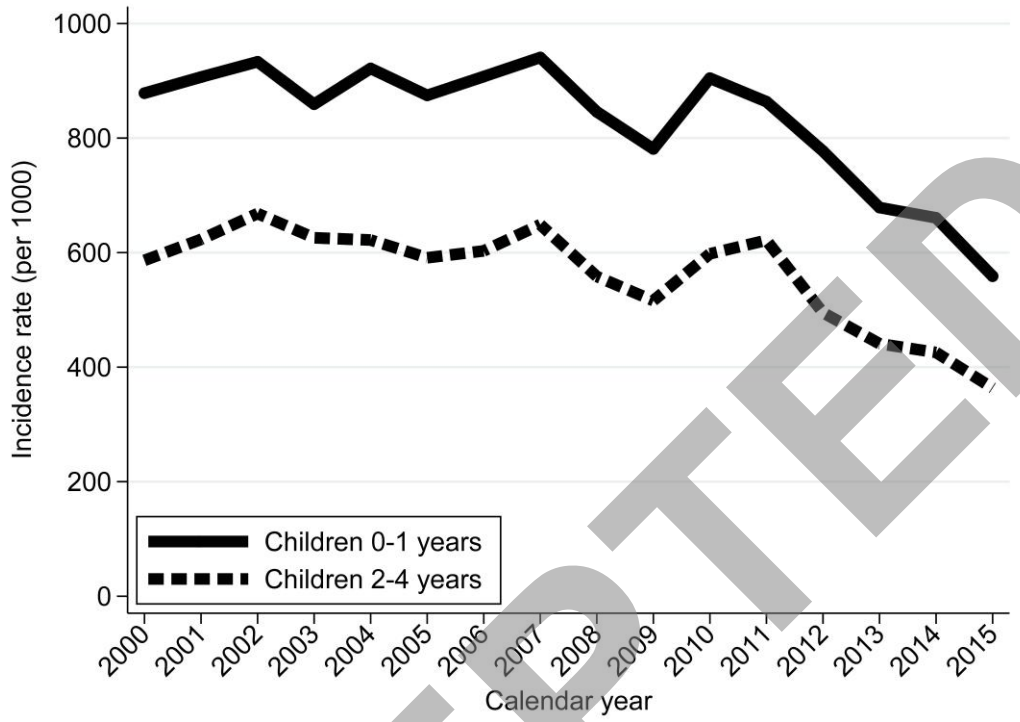

Figure 2

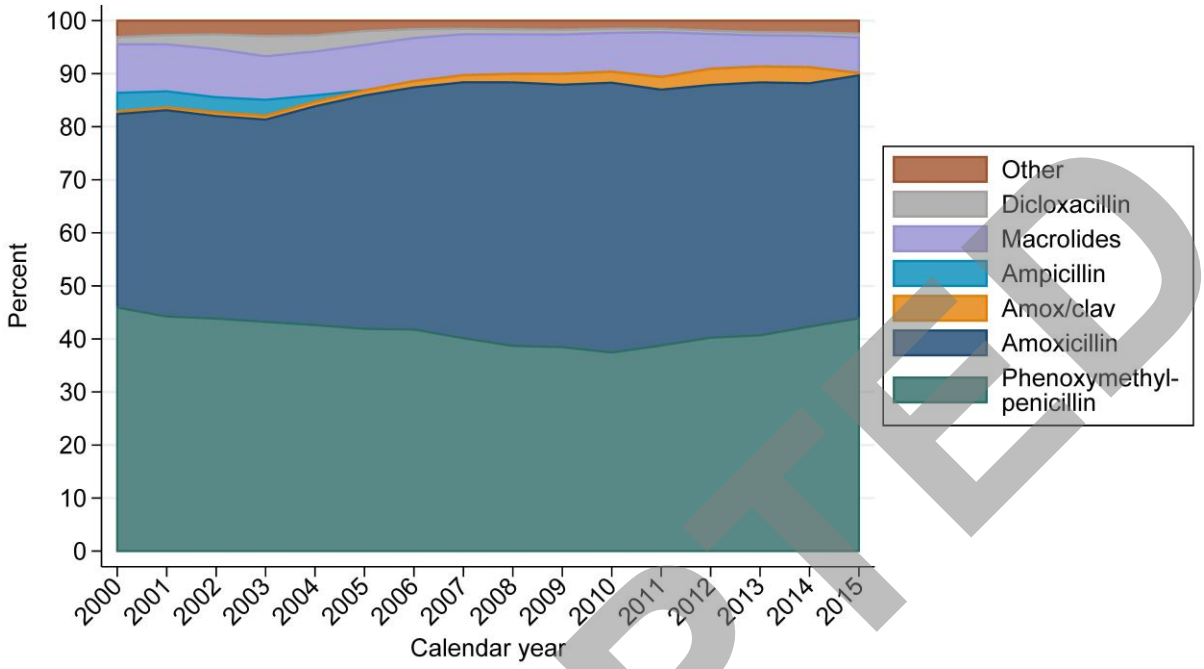

Figure 3

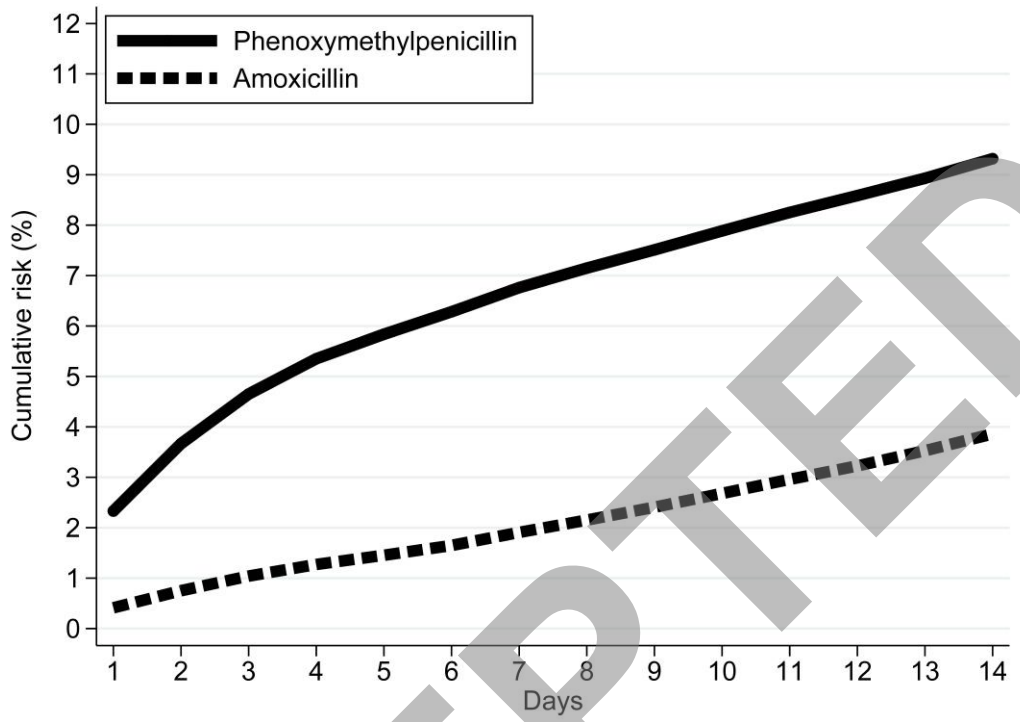

Figure 4