Antibiotic prescriptions to children with periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis

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ORIGINAL ARTICLE

Antibiotic prescriptions to children with periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis

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Abstract

Aim: To investigate the rate of dispensed antibiotic prescriptions to children and adolescents with PFAPA and compare this with the rate for children in the general population. Furthermore, to compare dispensed antibiotic prescription rates before and after a diagnosis of PFAPA was established.

Methods: Patients aged 0–17 years and diagnosed with PFAPA between 1 January 2006 to 31 October 2017 were included retrospectively. Data on dispensed drug prescriptions were obtained from the Swedish National Prescribed Drug Register.

Results: The PFAPA cohort received more antibiotic prescriptions than the general population in all but one of the age groups and time periods that were analysed. The largest difference was seen in 2014–2017 in the youngest age group (0–4 years) when children with PFAPA received 1218 antibiotic prescriptions per 1000 person years compared to 345 in the general population (IRR 3.5; 95% CI 2.8–4.4).

The yearly number of antibiotic prescriptions to PFAPA patients was reduced from 2.1 before diagnosis to 0.8 after diagnosis, a reduction of 62%.

Conclusion: This study shows higher rates of dispensed antibiotic prescriptions for children with PFAPA than in the general population. The reduction of prescriptions after an established PFAPA diagnosis indicates that antibiotics were previously incorrectly prescribed for PFAPA episodes.

KEYWORDS
adolescents, anti-bacterial agents, autoinflammatory disorders, child, periodic fever, prescriptions

1 | INTRODUCTION

Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) is an autoinflammatory syndrome that causes regularly recurring febrile episodes associated with one or more of the symptoms described by the acronym and distinctly elevated inflammatory markers. Although PFAPA syndrome primarily affects young children below the age of 5 years, the onset can also occur in older ages.[1,2] The fever episodes are self-limited, usually last 3–6 days and recur in a periodic manner with intervals of 3–5 weeks. Between

Abbreviations: ATC, Anatomical Therapeutic Chemical; IRR, incidence rate ratio; PFAPA, Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis.

fever episodes, patients with PFAPA are well, inflammatory markers normalise and children with the syndrome grow and develop normally.[3,4] The periodic fevers may persist for years but usually subside over time and eventually stop in most patients.[5]

The pathogenesis of PFAPA is still unknown but it is considered an autoinflammatory disease based on the clinical picture of periodic fevers, which is similar to the classical monogenic autoinflammatory disorders. Additionally, studies show a cytokine pattern compatible with activation of the innate immune system during fever, characteristic of autoinflammatory disorders, while hallmark features of autoimmunity such as autoantibodies and specific autoreactive T-cells are lacking.[6] No causative infectious agent has been found in PFAPA syndrome and antibiotics are ineffective.[3,7] Still, there is a risk that children with PFAPA unduly receive repeated courses of antibiotics, as the individual fever episode can be hard to distinguish from a bacterial infection such as streptococcal tonsillitis, pneumonia or pyelonephritis.

Overuse of antibiotics is problematic in several ways. On a population level, the selective pressure created by a broad use of antibiotics drives bacterial resistance,[8,9] and overuse of medications results in both direct costs for medications and indirect costs related to the associated medical consultations.[10] On an individual level, there is a risk of drug-inflicted side effects, and antibiotic exposure has been associated with a disruption of the gut microbiota and adverse long-term health outcomes.[11,12] A small Italian study of patients with PFAPA showed that 40% received more than 5 antibiotic prescriptions/year for symptoms coherent with PFAPA episodes.[13] Apart from that study, little is known regarding the frequency of antibiotic treatment in patients with PFAPA and how prescription rates are affected by a PFAPA diagnosis. The aim of this study was to investigate the rate of dispensed antibiotic prescriptions to children with PFAPA and compare this with the rates in children in the general population in defined age groups and time periods. Furthermore, to compare dispensed antibiotic prescription rates before and after the diagnosis of PFAPA was made.

Key notes

- Antibiotic prescriptions are dispensed to children with PFAPA to a significantly higher degree than to children in the general population, especially in the youngest age groups.
- Rates of dispensed antibiotic prescriptions decrease after a diagnosis of PFAPA is made.
- An increased recognition and timely diagnosis of PFAPA syndrome in children can contribute to a reduction of antibiotic prescriptions in this group.

2 | METHODS

2.1 | Data collection

A cohort of 336 children (0–17 years of age) who were diagnosed with PFAPA from 1 January 2006 to 31 October 2017 was identified in a previous study by our group.[14] The cohort represented all children diagnosed with PFAPA in three out of four paediatric units at hospitals in Region Västra Götaland during that time period. All patients in the cohort met the modified Marshall criteria,[3] with the exception that children with disease onset ≥5 years of age also were included. Data on dispensed drug prescriptions during the ages 0–19 years were obtained retrospectively for the PFAPA cohort from 1 January 2006 to 31 December 2017 from the Swedish National Prescribed Drug Register.[15] In Sweden, antibiotics are only available through prescription, and the register contains all drug prescriptions dispensed at pharmacies in Sweden linked to individuals by the Swedish personal identity numbers. The register is based on the Anatomical Therapeutic Chemical (ATC) classification system and antibiotics were defined as all drugs under the ATC-code J01 (excl. J01XX05 methenamine). Register data on an individual level were obtained for 333/336 patients in the original PFAPA cohort. The remaining three patients were excluded as they lacked complete Swedish personal identity numbers and could thus not be identified in the registry. For comparison, data on dispensed antibiotic prescriptions for the whole population in the defined age groups in Region Västra Götaland during the same time interval were also obtained from the Swedish National Prescribed Drug Register.[15] The metric 'dispensed antibiotic prescriptions per 1000 person years' was chosen to enable comparison between the PFAPA cohort and the general population. This metric was acquired directly from the registry for the general population and was calculated for the PFAPA cohort based on the registry data.

2.2 | Data analysis and statistics

Patients were divided into four age categories: 0–4, 5–9, 10–14 and 15–19 years. This age group classification was chosen since it is used in the National Prescribed Drug Register, as well as in many other studies of antibiotic use in the paediatric setting.[16] Over the observation period, members of the study population could contribute to more than one age category. In the PFAPA cohort, duplicate prescriptions of the same type of antibiotic issued within 3 days from the initial prescription were removed. As individual data were not available in the general population, this could not be done for that group. To enable analysis of changes in prescription rates over time, the different age groups were compared during the periods 2006–2009, 2010–2013 and 2014–2017, using incidence rate ratio (IRR).

In order to investigate whether antibiotic prescription rates changed after patients were diagnosed with PFAPA, the number of dispensed antibiotic prescriptions each patient received during 1 year before and 1 year after the time of the diagnosis was calculated. The number of prescriptions before and after PFAPA diagnosis was compared in the whole cohort and in subgroups based on the age at the time of PFAPA diagnosis, using the paired samples *T*-test or Wilcoxon Signed Rank Test, depending on group size. As antibiotics are more commonly prescribed in the youngest age groups and

antibiotic prescription rates have declined over time in the general population in Sweden,[17] linear regression was performed to investigate if there was a correlation between the change in antibiotic prescriptions and age at the time of diagnosis or the year the diagnosis was made. IBM SPSS Statistics (version 28.0.0.0) was used for statistical analyses. All statistical tests were two-tailed and $p < 0.05$ was defined as significant.

3 | RESULTS

Among the 333 PFAPA patients included in the study, 176 (52.9%) were boys and 157 (47.1%) girls. The median age of onset of PFAPA was 2.0 (range 0.1–16.0) years and median age at the time of diagnosis was 4.4 (range 0.75–17.9) years. Further characteristics of the cohort have been previously published.[14] The general population in the Region Västra Götaland consisted in 2006 of 365 669 persons between 0 and 19 years of age (51.4% male and 48.6% female) and in 2017 of 381 584 persons (51.6% male and 48.4% female).

3.1 | Individuals with PFAPA receive more antibiotics than the age-matched general population

The PFAPA cohort received more antibiotic prescriptions than the general population in all age groups and time periods that were analysed (Table 1; Figure 1). The highest rate of dispensed antibiotic prescriptions was seen in the youngest group of children (0–4 years of age) with PFAPA in 2006–2009 (1369 per 1000 person years). This age group and time period also showed the highest rate of antibiotic prescriptions in the general population (663 per 1000 person years), but the PFAPA cohort received 2.1 times as many prescriptions (95% CI 1.8–2.4).

Rates of dispensed antibiotic prescriptions remained highest in the youngest age group (0–4 years) and lowest in the age group 10–14 years in all time periods, with an overall trend towards decreasing prescription rates over time (Figure 1). Nonetheless, while antibiotic prescriptions decreased over time in all age groups in the general population, this was not seen in the youngest and oldest age groups of patients with PFAPA. In 2014–2017, the youngest children with PFAPA received 1218 antibiotic prescriptions per 1000 person years compared to 345 in the general population, resulting in a ratio of 3.5 (95% CI 2.8–4.4), which was higher than in the previous time periods.

3.2 | β-lactam antibiotics constituted the majority of prescriptions

The most frequently dispensed antibiotic in the PFAPA cohort as well as in the general population in the age group 0–19 years was phenoxymethylpenicillin, followed by amoxicillin +/− β-lactamase

TABLE 1 Dispensed antibiotic prescriptions to the PFAPA cohort and the general population in Region Västra Götaland in different time periods and age groups.

Time periods and age groups	No. of PFAPA person years*	No. of prescriptions PFAPA cohort	No. of ab /1000 person years PFAPA cohort	No. of ab/1000 person years general pop.	IRR (95% CI)
2006–2009					
0–4	488	668	1369	663	2.1 (1.8–2.4)
5–9	204	223	1093	462	2.4 (1.8–3.1)
10–14	47	16	340	224	1.5 (0.6–4.0)
15–19	9	9	1000	369	2.7 (0.7–10)
2010–2013					
0–4	522	589	1128	506	2.2 (1.9–2.6)
5–9	440	299	680	384	1.8 (1.4–2.2)
10–14	161	74	460	204	2.3 (1.4–3.6)
15–19	34	7	206	317	0.7 (0.2–2.9)
2014–2017					
0–4	261	318	1218	345	3.5 (2.8–4.4)
5–9	537	251	467	266	1.8 (1.4–2.3)
10–14	380	78	205	153	1.3 (0.9–2.1)
15–19	121	72	595	248	2.4 (1.5–3.8)

Note: The number of dispensed antibiotic prescriptions per 1000 person years in the different time periods were calculated in the PFAPA cohort and the general population in Region Västra Götaland, respectively. Over the observation period, members of the study population could contribute to more than one age category.

Abbreviations: Ab, dispensed antibiotic prescriptions.

*As most children were young when they were diagnosed with PFAPA, the oldest age groups were small in 2006–2009, but became larger over time as the children in the cohort aged. The numbers in this column represent the accumulated person years in the specified time periods and age groups.

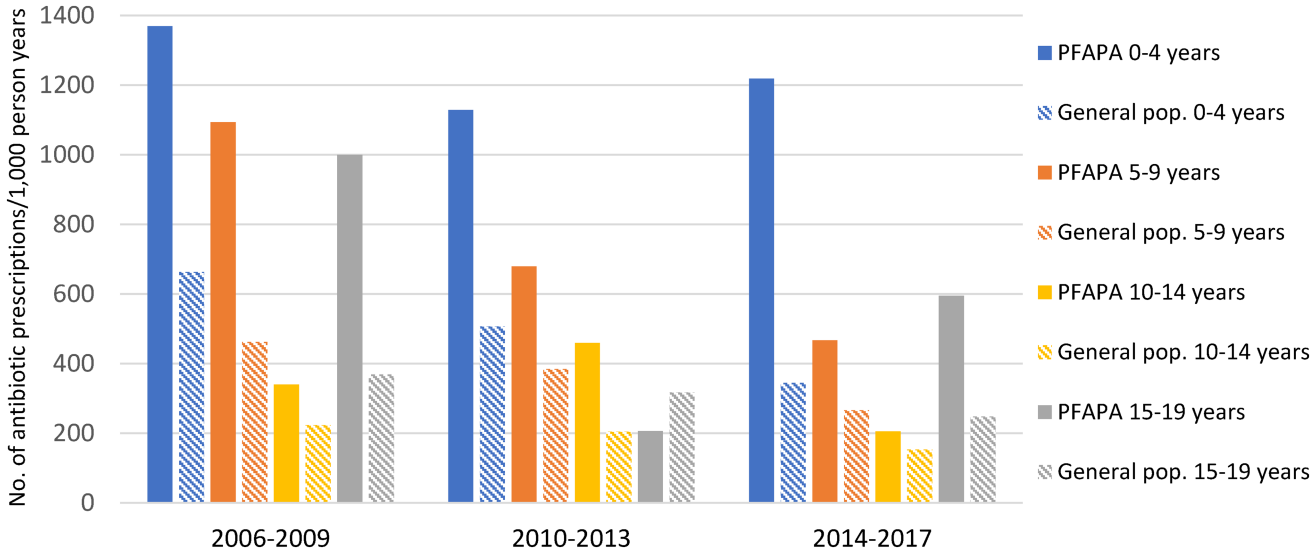

FIGURE 1 Dispensed antibiotic prescriptions per 1000 person years in the PFAPA cohort and the general population in Region Västra Götaland in different time periods and ages.

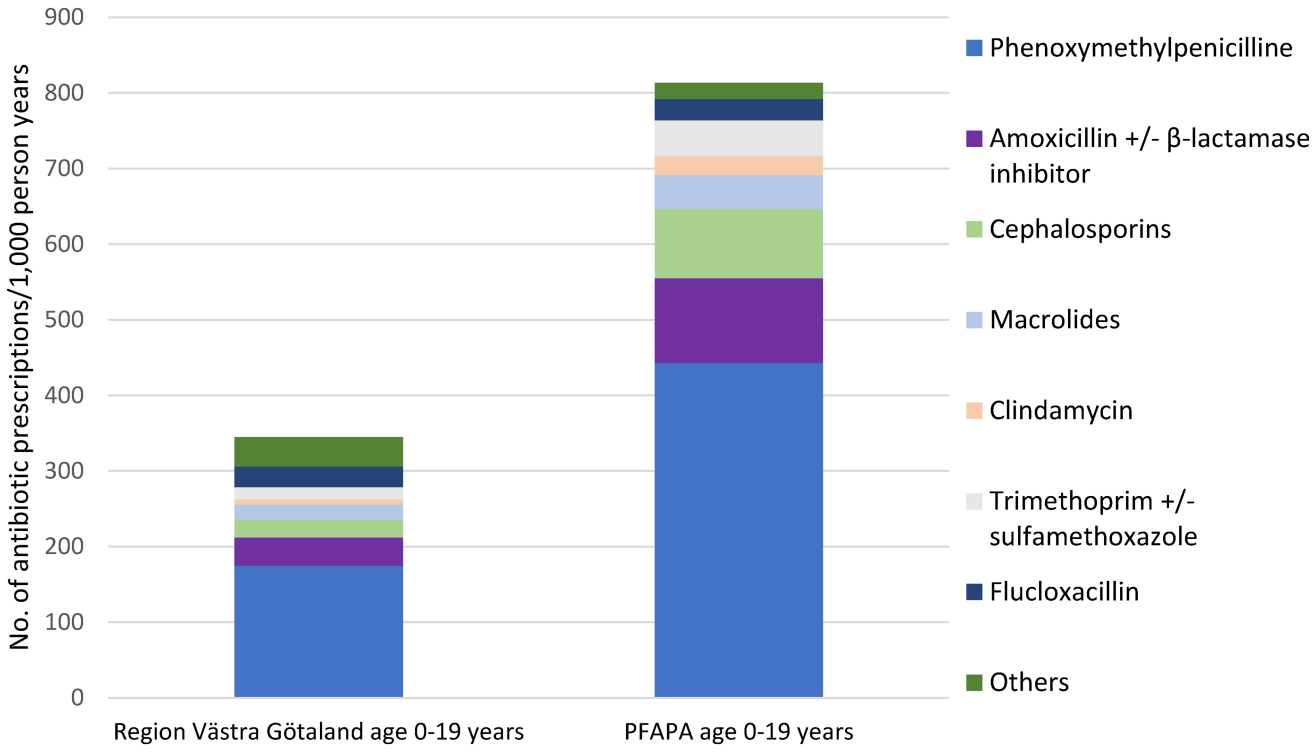

FIGURE 2 Dispensed antibiotic prescriptions/1000 person years in 2006–2017 in ages 0–19 years in the general population and the PFAPA cohort, sorted by substance.

inhibitor (Figure 2). Together, these substances constituted 62% of dispensed antibiotic prescriptions in 0–19-year-olds in the general population and 68% in the PFAPA cohort. Cephalosporines represented 11% of dispensed antibiotic prescriptions in the PFAPA group and 7% in the general population in the same age group. In absolute numbers, this corresponded to four times as many dispensed prescriptions of cephalosporines in the PFAPA cohort as in the general population (92 vs. 23 per 1000 person years).

3.3 | The number of dispensed antibiotic prescriptions is reduced following PFAPA diagnosis

Data on dispensed antibiotic prescriptions 1 year before and 1 year after the time the PFAPA diagnosis was established were available for 317/333 patients. The patients were aged 0–17 years at the time of diagnosis. The mean number of antibiotic prescriptions they

TABLE 2 Dispensed antibiotic prescriptions 1 year before versus after a diagnosis of PFAPA in different ages.

Age at diagnosis	No. of patients	No. of ab 1 y before diagnosis	No. of ab 1 y after diagnosis	*p*-values
0–17	317	2.1 (2.2)[a]	0.8 (1.3)[a]	<0.001
0–4	198	2.5 (2.3)[a]	1.0 (1.4)[a]	<0.001
5–9	95	1.6 (1.7)[a]	0.4 (0.9)[a]	<0.001
10–14	14	0 (0–2)[b]	0 (0–1)[b]	0.02
15–17	10	0 (0–9)[b]	0 (0–1)[b]	0.2

Note: Data were available for 317/333 patients. Paired T-test was used for comparison in the whole cohort and the two youngest age groups, while the Wilcoxon Signed Rank Test was used in the two oldest age group, due to low numbers of patients.

[a]Mean (SD).

[b]Median (range).

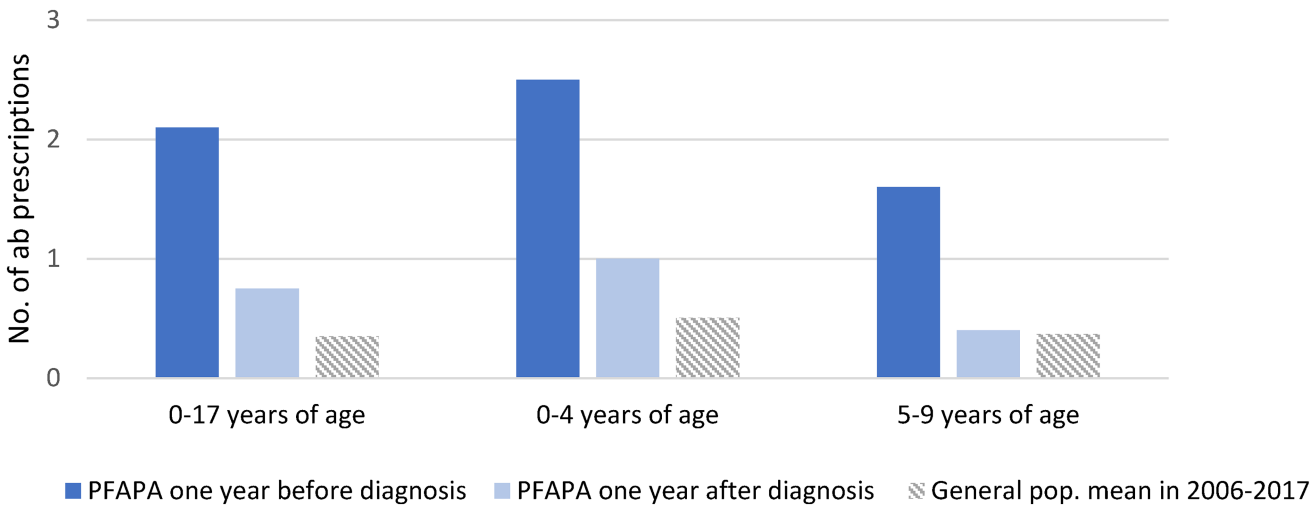

FIGURE 3 Mean number of dispensed antibiotic prescriptions per individual in 1 year.

received per year decreased from 2.1 (95% CI 1.9–2.4) 1 year before diagnosis to 0.8 (95% CI 0.6–0.9) 1 year after diagnosis ($p < 0.001$), a reduction by 62%. The linear regression analysis showed that the outcome was affected neither by the age at the time of diagnosis (β −0.47, 95% CI −0.12—0.02, $p = 0.19$) nor by the year of diagnosis (β −0.08, 95% CI −0.15—0.003, $p = 0.06$). When the cohort was divided into subgroups based on age, significant differences were seen in all age groups except the oldest (15–17 years; Table 2), but this group consisted of only 10 patients. In the general population in Region Västra Götaland, the mean annual number of antibiotic prescriptions per child in 2006–2017 was 0.35 (SD 0.08) among all children 0–17 years, 0.50 (SD 0.14) in the age group 0–4 years and 0.37 (SD 0.09) in the age group 5–9 years (Figure 3).

4 | DISCUSSION

This study shows that antibiotic prescriptions are dispensed to children with PFAPA syndrome to a significantly higher degree than to children in the general population. In the two youngest age groups (0–4 and 5–9 years), children diagnosed with PFAPA consistently received significantly more antibiotic prescriptions than their age-matched counterparts in the general population across all three analysed time periods. Notably, rates of antibiotics to children with PFAPA in the youngest age group remained high throughout the study period despite the decrease seen over time in the general population. Consequently, in this age group, children with PFAPA received 2.1–3.5 times more antibiotic prescriptions than children in the general population. In the two oldest age groups, significant differences were seen in some but not all analysed time periods, with less robust results in these age categories due to smaller numbers of patients.

Furthermore, the study shows that the numbers of dispensed antibiotics to children with PFAPA decreased by 62% after the diagnosis was made. This decline is likely mainly attributable to the awareness among families and physicians that PFAPA causes the child's fever episodes and that antibiotics are ineffective in managing these fevers. Other contributing factors may include the initiation of specific treatments (such as colchicine or tonsillectomy) post-diagnosis, resulting in a decrease in frequency or severity of fever episodes, or the natural course of the disorder leading to a gradual subsiding of fever episodes. Despite the decline in

dispensed prescriptions following diagnosis, there appears to be a persistent elevation of antibiotic rates for children with PFAPA even 1 year after the diagnosis, in comparison to children in the general population. Although the mean absolute numbers of dispensed antibiotics are low, and the causes of these prescriptions cannot be fully elucidated in this study, this suggests ongoing overprescription post PFAPA diagnosis, as previously shown by Costagliola.[13] If this is the case, it underscores the importance of providing repeated information about the disorder and its treatment to both families and healthcare providers, aiming to further reduce unnecessary prescriptions.

In Sweden, a coordinated national effort to control microbial resistance to antibiotics has resulted in decreased antibiotic use for outpatients since the launch of the Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (Strama) in 1995,[18] and prescription rates remain low compared to the EU/EEA population-weighted mean.[19] This is reflected in the overall decrease in antibiotic prescription rates over time in both the PFAPA group and in the general population in this study. The persistently high antibiotic prescription rates to young children with PFAPA are probably due to the highly inflammatory clinical presentation of these children, with high fever, distinctly elevated inflammatory markers such as CRP, and often a clinical picture of acute tonsillitis.[14,20,21] The relatively high risk of severe bacterial infection/sepsis among the youngest children might prompt physicians to adopt more liberal antibiotic prescription practices for this group, even though streptococcal tonsillitis is rare among them.[22]

Phenoxymethylpenicillin was the most common antibiotic in both the PFAPA group and in the general population. This is in accordance with recommendations from the Public Health Agency of Sweden, who publish treatment recommendations for common infections in primary care in cooperation with Strama and the Swedish Medical Products Agency.[23] The recommendations provide support in decision-making regarding both when antibiotics are indicated and what substance to use. Phenoxymethylpenicillin is recommended as first-line treatment for acute otitis media, pharyngotonsillitis, community-acquired pneumonia and erysipelas in these guidelines. The high proportion of antibiotics typically used for airway infections in the PFAPA cohort suggests that symptoms compatible with such infections were the most common indications for prescription.

The data on dispensed antibiotic prescriptions in this study are robust, as the National Drug registry is population-based and comprehensive. The exclusion of duplicate prescriptions in the PFAPA group might have resulted in an underestimation of the differences between this group and the general population, but we believe this was necessary to provide an accurate account of the antibiotic consumption in the PFAPA group. While the register-based data used in this study allow us to investigate the rates of dispensed antibiotics and proportion of different substances, data on the medical indication for the prescriptions were not available. Thus, we cannot determine whether the antibiotic prescriptions were made due to symptoms compatible with PFAPA episodes or attributed to other conditions, but the reduction of prescriptions after the PFAPA diagnosis was made gives reason to believe that antibiotics were previously incorrectly prescribed for PFAPA episodes. Future studies are needed to determine infection rates in children with PFAPA and whether they differ from children in the general population in this respect.

The overuse of antibiotics and the associated increase of bacterial resistance is a global threat to future health.[24] The results of this study indicate that an increased recognition and timely diagnosis of PFAPA syndrome in children can contribute to a reduction of antibiotic prescriptions in this this group. This would have positive effects for the individual patients, and even though PFAPA syndrome is relatively rare, increased awareness of the syndrome could also highlight the importance of considering alternative diagnoses to bacterial infections in children with repeated febrile episodes.

AUTHOR CONTRIBUTIONS

Karin Rydenman: Conceptualization; investigation; writing – original draft; methodology; writing – review and editing; visualization; formal analysis; project administration. **Stefan Berg:** Conceptualization; writing – review and editing; methodology; supervision. **Anna Karlsson-Bengtsson:** Conceptualization; writing – review and editing; supervision. **Anders Fasth:** Conceptualization; funding acquisition; methodology; supervision; writing – review and editing; validation. **Per Wekell:** Conceptualization; investigation; funding acquisition; methodology; supervision; validation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

None declared.

ETHICAL APPROVAL

The study was approved by the Swedish Ethical Review Authority (reference number 2020-03549 and2020-05797).

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