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Trajectories of antibiotic prescriptions in Italian children in the first four years of life: a retrospective birth-cohort study

Isabella Rosato[1,2], Gloria Porcu[1,2], Daniele Donà[3], Erich Batzella[1], Carlo Giaquinto[4], Anna Cantarutti[2*] and Cristina Canova[1]

Abstract

Background Antibiotics are among the most frequently prescribed medications for pediatric patients. Inappropriate use, particularly in the first years of life, can contribute to the development of antibiotic resistances and impact the maturation of the gut microbiome. Describing prescription patterns using nationally collected data is essential for identifying or monitoring existing strategies for reducing excessive use. This study aims to identify antibiotic prescription trajectories during the first four years of life and to investigate their association with sociodemographic factors.

Methods In this retrospective cohort study, we used data collected through the Pedianet registry, a monitoring system involving approximately 200 family pediatricians (FPs) in Italy. We considered children born between 2004 and 2018 with complete follow-up during their first four years of life, excluding those with a birth weight of < 2500 g, gestational age < 37 weeks or genetic disorders. Prescription trajectories over the 16 trimesters of observation were estimated using Group-Based Trajectory Modelling (GBTM), by classifying the included children into homogeneous groups based on their probabilities of membership. The association between trajectories and sociodemographic factors was examined with multinomial logistic regression with random intercepts for FPs.

Results A total of 143,098 children born between 01/01/2004 and 31/12/2018 were included. Between 0 and 4 years of age, these children received a total of 684,010 antibiotic prescriptions. GBTM identified four different trajectories, defined as: [1] "very low use" of antibiotics (34.9% of children) [2], "low-to-moderate use" (22.8%) [3], "moderate-to-low use" (28.0%) and [4] "high use" (14.3%). Compared to the "very low use" trajectory, male subjects residing in the center and south of Italy and born between 2004 and 2008 had a higher probability of belonging to trajectory groups with "moderate-to-low use" and "high use".

Conclusions From 2004 to 2022 in Italy, we observed heterogeneous antibiotic prescription patterns among children aged 0–4 years. Future strategies aimed at reducing the number of prescriptions in this age group should target the subgroups at higher risk.

Keywords Antibiotic prescriptions, Group-based trajectory modelling, Pedianet, Family pediatrician

*Correspondence:
Anna Cantarutti
anna.cantarutti@unimib.it

Full list of author information is available at the end of the article

Introduction

Antibiotics are the most prescribed medications for infants and children [1, 2]. Regrettably, antibiotics are frequently prescribed unnecessarily in both community and hospital settings. In the community, a significant proportion of children receive antibiotics for viral infections, such as colds or bronchitis [3, 4]. In hospitals, prolonged courses of broad-spectrum antibiotics contribute to the escalation of antimicrobial resistance.

The excessive, unnecessary, and inappropriate use of antibiotics is linked to elevated rates of antibiotic resistance, significantly impacting populations across all age groups, particularly children [5, 6]. Drug-resistant bacterial infections pose a significant global health threat, resulting in an estimated 200,000 newborn deaths annually and causing substantial illness and mortality across all age demographics [7]. Notably, high estimates of attributable deaths and disability-adjusted life years at the European level have been reported, particularly among infants in Italy and Greece [8, 9]. Furthermore, antibiotic resistance profoundly affects healthcare systems, leading to increased costs and resource utilization [10].

Antibiotic misuse and overuse in the first years of life can also impact microbiome transmission and disrupt its early-life maturation [11], with potential lasting health consequences [12, 13]. Several epidemiological studies linked exposure to antibiotics in children to an increased risk of developing certain health problems, including asthma, wheezing, skin conditions like psoriasis and atopic dermatitis, and other immune-related diseases [14, 15].

Various studies conducted in Italy have investigated antibiotic dispensing rates in hospitalized children [16–18] and also in primary care settings [19–22].

The most recent National Report on antibiotic use in Italy highlights a progressive increase in antibiotic use among the pediatric population, noting that children in the youngest age groups, particularly those aged 2 to 5 years, are the most exposed to antibiotic prescriptions. Moreover, the report shows significant heterogeneity with respect to geographic location, with children from Northern Italy receiving fewer antibiotic prescriptions than those from Southern Italy [23]. Regional differences in prescribing patterns are not limited to overall prevalence but also extend to the choice of antibiotic class. Children in Northern Italy tend to receive prescriptions that are more consistent with clinical guidelines, whereas in Southern Italy, there is a higher use of antibiotics associated with an increased risk of resistance [23]. Nevertheless, extensive and representative data are still required to comprehensively monitor and describe prescription patterns and their changes over time in Italy.

This study aims to improve our knowledge of antibiotic prescribing practices for young children in Italian primary care settings. We analyze data from Pedianet, a national pediatric database, to identify trends in antibiotic prescriptions for Italian children during the first four years of their lives. We hypothesize that antibiotic prescriptions in this time frame do not follow a uniform pattern, but rather distinct trajectories that vary according to sociodemographic and geographic factors. This up-to-date and comprehensive data will hopefully inform strategies for future stewardship intervention and more appropriate antibiotic use in Italy.

Methods

Study design and population

This retrospective, observational, birth-cohort study analyzed data from the Pedianet network (https://pedianet.it/), a national database established in 1998. Pedianet collects information on routine healthcare provided by over 400 family pediatricians (FPs) in Italy for a large population of children [24]. The network comprises almost 3% of the Italian pediatric population [25], with family physicians distributed across various Italian regions contributing anonymized data regarding their patients' health status, medications, demographic characteristics, and clinical conditions to the database. Parents or legal guardians provide informed written consent for their children's inclusion in the database and data collection.

For the present analysis, we included all children aged 0–4 years born between January 1, 2004 and December 31, 2018, forming part of the Pedianet database and for whom complete follow-up data for the first 4 years of life was available. We included children born up to December 31, 2018, because the end of the 4-year follow-up for these children coincided with the moment when data extraction from Pedianet was performed. Complete follow-up was defined as continuous care by the same Pedianet FP from birth to four years of age, with uninterrupted registration in the Pedianet database throughout this period. We excluded children with incomplete follow-up, including those who exited the Pedianet network due to death or other reasons, changed FP, relocated to a different region, those with a birthweight of less than 2500 g or a gestational age of less than 37 weeks ($n = 9742$) as well as those affected by genetic disorders (such as achondroplasia, Prader-Willi, Turner, Williams, Cornelia De Lange, or Down Syndrome, $n = 83$) (Figure S1).

We collected information for each child regarding their sex, birth year and region of residence. Birth year was categorized into three cohorts (2004–2008, 2009–2013, 2014–2018) to smooth annual fluctuations in prescription rates, facilitating more stable estimation of temporal trends, and to reflect changes in key approaches to antibiotic use in Italy, with the last period corresponding to the initial implementation of national antibiotic stewardship programs [26]. The residence was further categorized into five areas: Northeast (Friuli-Venezia Giulia or Veneto), Northwest (Lombardy, Piedmont, Liguria), Central (Tuscany, Lazio, Marche, Abruzzo), and Southern (Campania, Puglia, Sardinia, or Sicily) Italy. This categorization was adopted to facilitate interpretation of the results and to align with classifications employed in national reports on antibiotic use. Information regarding parental socio-economic status was provided by measuring the area deprivation index (ADI). The ADI describes social and material deprivation; it is calculated based on the 2011 General Census of Population and Housing data, by taking into consideration the following five items: (1) a low level of education, (2) unemployment, (3) non-home ownership, (4) one parent family, and (5) overcrowding [27, 28]. The addresses of the children included in the study were georeferenced and associated with the census block of each Italian municipality. By linking the addresses of the children included in the study to the census block number, we determined the corresponding area deprivation index, which was categorized using quintiles on the regional level. A deprivation index in the 1 st quintile indicates a higher socio-economic status, whereas a deprivation index in the 5th quintile indicates the lower socio-economic scenario.

Antibiotic prescriptions

Antibiotic prescriptions provided for children included in the study by their FPs were identified and considered as proxies of antibiotic use. Antibiotics were defined based on the Anatomical Therapeutic Chemical (ATC) classification [29] considering the following antibiotic therapy classes: penicillins (codes J01CA, J01CA01, J01CA04, J01CR01, J01CR02, J01CR04, J01CA06, J01CA12, J01CE, J01CE01, J01CE08, J01CF05, J01CR05), cephalosporins (codes J01DB01, J01DC02, J01DC04, J01DC06, J01DC10, J01DD01, J01DD02, J01DD04, J01DD08, J01DD13, J01DD14, J01DE01, J01DB04, J01DD09, J01DD16), macrolides (codes J01FA01, J01FA02, J01FA06, J01FA07, J01FA09, J01FA10, J01FA11, J01FA12) and a class formed by antibiotics not included in the first three groups ("Others").

Statistical analysis

Descriptive characteristics of the study group were presented using frequencies and proportions for categorical variables and mean and standard deviation or median and interquartile range for continuous variables.

Group-based trajectory modelling (GBTM) was used to classify children according to their antibiotic prescription patterns over time. GBTM is a semi-parametric method for analyzing longitudinal data, that identifies latent (unobserved) subgroups of subjects following similar outcome patterns, allowing for heterogeneity in behaviors [30]. Using maximum likelihood estimation (MLE), GBTM simultaneously estimates the parameters of the polynomial functions representing each trajectory group, and the probability of group membership for each child among the identified trajectories.

To conduct GBTM, we first defined specific time windows by dividing the 4-year observation time available for each child into 16 trimesters. A categorization into trimesters was chosen to provide sufficient temporal resolution while maintaining statistical stability. For each trimester, the outcome of interest was exposure to antibiotic prescriptions, classified as a dichotomous variable indicating whether at least one prescription was recorded by the FP during the period considered. The presence of multiple prescriptions within the same trimester was treated equivalently to one prescription. To determine the most appropriate number of trajectory groups, we fitted models with increasing numbers of groups, ensuring that each group included at least 5% of the total population [30]. We selected the model minimizing the Bayesian Information Criterion (BIC) values. The same approach was applied to identify the most suitable polynomial order (linear, quadratic or cubic) for each trajectory. We began with linear forms and incrementally tested higher-order terms, selecting the final model based on a combination of statistical and substantive criteria: the lowest BIC, an average posterior probability of group membership ≥ 0.70 for each group, and meaningful clinical interpretability of the identified trajectories [31, 32]. A trajectory curve for each group was finally estimated, together with probabilities of group membership for each child included in the study. Each child was assigned to the trajectory group corresponding to their highest posterior probability. The identified trajectory groups were graphically represented in a plot with time (in trimesters) on the x-axis and the probability of prescription on the y-axis, and each trajectory was labeled according to its key characteristics.

We furthermore used the $\chi 2$ test to compare the distribution of categorical variables between different trajectory groups. We evaluated the association between all the included socio-demographic factors and trajectory memberships using multinomial logistic regression, including a random intercept for each FP to account for within-cluster correlation and unmeasured heterogeneity among FPs. In this analysis, we estimated odds ratios (ORs) and corresponding 95% confidence intervals for each trajectory membership compared to the reference trajectory, the one with the lowest exposure to antibiotic prescriptions in the observation period ("very low use"). We conducted both unadjusted and adjusted models, including only children with complete data for the following covariates, categorized as described above: sex, area of residence, birth cohort, and deprivation index quintile.

Table 1 Socio-demographic characteristics and distribution of antibiotic prescriptions in the observation period for included subjects ($n = 134098$)

	Number of antibiotic prescriptions in the first 4 years of age		
	Mean (SD)	**Median (1st –3rd quartile)**	**Min-max**
Sex			
F ($n = 64491$)	4.5 (4.8)	3 (1–6)	0–67
M ($n = 69607$)	5.0 (5.2)	4 (1–7)	0–68
Area of residence			
Northeast Italy ($n = 59521$)	3.7 (3.8)	3 (1–5)	0–63
Northwest Italy ($n = 18531$)	4.0 (3.8)	3 (1–6)	0–53
Central Italy ($n = 19103$)	5.3 (5.0)	4 (2–8)	0–63
Southern Italy ($n = 36943$)	6.6 (6.5)	5 (2–10)	0–68
Birth cohort			
2004–2008 ($n = 50646$)	5.0 (5.4)	4 (1–7)	0–64
2009–2013 ($n = 50897$)	4.8 (4.9)	4 (1–7)	0–67
2014–2018 ($n = 32555$)	4.3 (4.5)	3 (1–6)	0–68
Deprivation index quintile			
1 st ($n = 22295$)	4.3 (4.5)	3 (1–6)	0–52
2nd ($n = 23604$)	4.7 (4.8)	3 (1–7)	0–68
3rd ($n = 24832$)	4.9 (5.2)	4 (1–7)	0–62
4th ($n = 23092$)	5.0 (5.1)	4 (1–7)	0–63
5th ($n = 21621$)	5.0 (5.4)	3 (1–7)	0–63
Missing ($n = 18654$)	4.6 (5.1)	3 (1–7)	0–67
Total			
($n = 134098$)	4.8 (5.0)	3 (1–7)	0–68

Table 2 Total number of antibiotic prescriptions in the 4-years observation period for included subjects, by antibiotic class ($n = 684010$)

	Females	**Males**	**Total**
Therapy class			
Penicillins	171,817 (54.7%)	204,254 (55.2%)	376,071 (55.0%)
Cephalosporins	72,094 (23.0%)	83,078 (22.4%)	155,172 (22.7%)
Macrolides	61,323 (19.5%)	74,356 (20.1%)	135,679 (19.8%)
Others	8619 (2.8%)	8469 (2.3%)	17,088 (2.5%)
Total	313,853 (100.0%)	370,157 (100.0%)	684,010 (100.0%)

Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, North Carolina, US). The *TRAJ* procedure was used to implement GBTM, the *GLIMMIX* procedure was used to fit multinomial logistic regression models including random intercepts. P-values < 0.05 were considered statistically significant. This study was conducted in accordance with the Strengthening Reporting of Observational Studies in Epidemiology (STROBE) guidelines [33].

Results

Overall, we included 134,098 subjects forming part of the Pedianet cohort born between 2004 and 2018, 64,491 males (48.1%) and 69,607 females (51.9%). Most of them resided in Northeast Italy ($n = 59521$, 43.1%) and Southern Italy ($n = 36943$, 27.5%) and were born between 2004 and 2013 ($n = 101543$, 75.5%) (Table 1). Our cohort comprised almost 2.0% of all children born in Italy between 2004 and 2018 (National Institute of Statistics; ISTAT).

Table 1 also shows how antibiotic prescriptions varied among children during their first four years of life, stratified according to sex, area of residence, birth cohort and area deprivation index. Included children received a median of 3 (1st –3rd quartile = 1–7) antibiotic prescriptions. The highest recorded prescriptions were 67 for girls and 68 for boys. Children from Central and Southern Italy had a higher median number of antibiotic prescriptions compared to those born in Northern Italy. In addition, children born between 2014 and 2018 received fewer prescriptions at the middle point compared to those born between 2004 and 2008 (Table 1).

In this cohort, we identified a total of 684,010 antibiotic prescriptions (370157 in males, 684010 in females) in the 4-year study period. Most of the prescriptions were for penicillins (55.0%), followed by cephalosporins (22.7%) and macrolides (19.8%) (Table 2).

Table S1 shows the cumulative number of children who received at least one antibiotic prescription in the periods of interest, stratified according to sex, area of residence, birth cohort and area deprivation index. Up to 12 months of age, 58,353 children (43.5% of the total population) had received at least one antibiotic prescription; up to 4 years of age, 112,838 children (84.1% of included children) received at least one antibiotic prescription (Table S1).

To identify trajectories of antibiotic prescriptions in the first four years of life, we divided the total period of observation into 16 trimesters, and the presence of at least one prescription in each trimester was evaluated for each subject included in the study.

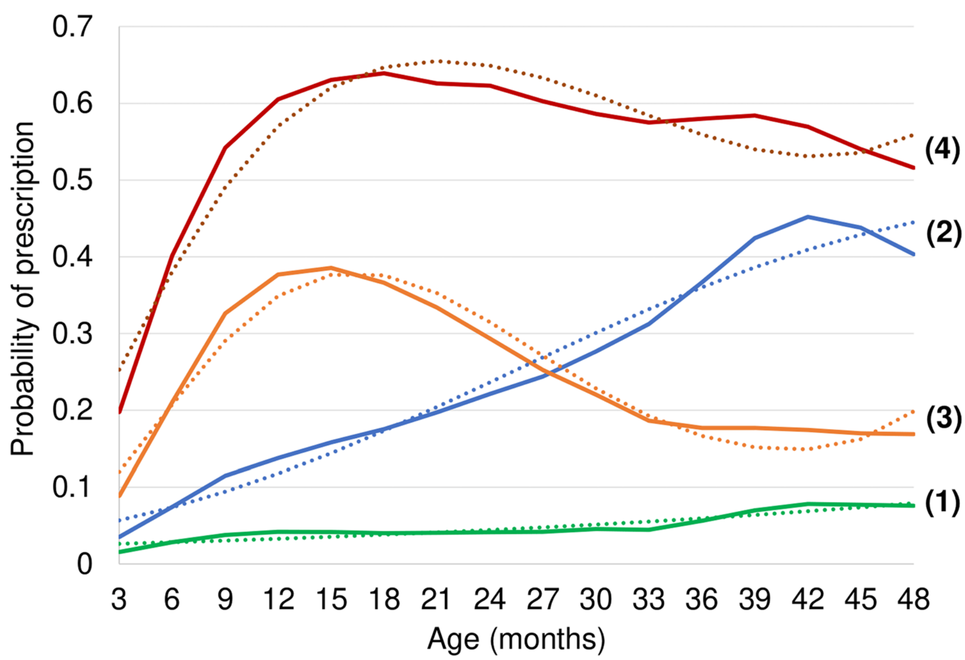
Table S2 shows the number of children with at least one antibiotic prescription registered in each of the trimesters considered for GBTM. In the first trimester of life, 6.8% of children received at least one antibiotic prescription. From 9 to 48 months, the percentage of children receiving at least one antibiotic prescription remained relatively stable, ranging from 22.8% to a peak of 26.8% between 39 and 42 months of life (Table S2).

A 4-group trajectory solution, employing linear and quadratic functions to describe the first and second groups, respectively, and a cubic function to describe the third and fourth groups, showed the best fitting, minimizing BIC and enabling an adequate repartition of included subjects (Table S3).

The four different antibiotic prescription trajectories identified using GBTM were categorized as follows: [1] very low use of antibiotics (34.9% of included children) [2], low-to-moderate use of antibiotics (22.8% of included children) [3], moderate-to-low use of antibiotics (28.0% of included children) and [4] high use of antibiotics (14.3% of included children) in the first four years of life (Fig. 1). Group [1] comprises children with consistently low antibiotic use over the study period, whereas group [4] comprises children highly exposed to antibiotic prescriptions from the first months of life onward. Groups [2] and [3] exhibit contrasting patterns of prescriptions. In group [2], children are more exposed to antibiotics during the first two years of life, followed by a decrease in exposure during the third and fourth years. In contrast, children in group [3] show an opposite pattern of exposure, with lower exposure to antibiotics in the first two years and prescriptions increasing during the third and fourth years of life.

We found significant differences in subjects' characteristics among the trajectory groups (p-value < 0.001 for all the associations, tested using the $\chi 2$ test). Children belonging to the first group ("very low use of antibiotics") were more likely to reside in Northeast Italy (52.1%) and to have higher socioeconomic status (55.1% in the 1 st −2nd ADI quintile). Children from the fourth group ("high use of antibiotics") were more often males, as well as children in group 2 and 3 ("Low-to-moderate" and "moderate-to-low" use). In addition, they were more likely to reside in Southern Italy (50.6%), to be born between 2004 and 2013 (80.4%), and to have a lower socioeconomic status (26.1% in the 5th ADI quintile, compared to 12.6% in the "very low use" group) (Table 3).

Table 4 shows how various factors are associated with membership in different antibiotic use groups ("very low use", "low-to-moderate use", "moderate-to-low use" and "high use"). The odds of belonging to the "low-to-moderate use" vs the "very low use" trajectory were higher for males and children residing in Central Italy compared to



Group	N (%)
(1) Very low use	46,823 (34.9%)
(2) Low-to-moderate use	30,542 (22.8%)
(3) Moderate-to-low use	37,489 (28.0%)
(4) High use	19,244 (14.3%)

Fig. 1 Trajectories of antibiotic prescriptions identified using GBTM. Notes: Children in group (1) show a pattern of very low use of antibiotics across the period of observation; children in group (2) show reduced use up to 24 months of age, followed by increased use; children in group (3) show an opposite pattern to those in group (2); children in group (4) are highly exposed to antibiotic across the whole period of observation. For each trajectory group, the solid line represents the model-estimated trajectory, while the dotted line represents the observed mean values at each time point, illustrating the fit of the model to the actual observations

Table 3 Socio-demographic characteristics of included children, overall and by trajectory group identified using GBTM

	Overall *N* = 134,098	Group 1 Very low use *N* = 46,823	Group 2 Low-to- moderate use *N* = 30,542	Group 3 Moderate-to- low use *N* = 37,489	Group 4 High use *N* = 19,244
Sex					
Female	64,491 (48.1%)	23,533 (50.3%)	14,974 (49.0%)	17,465 (46.6%)	8519 (44.3%)
Male	69,607 (51.9%)	23,290 (49.7%)	15,568 (51.0%)	20,024 (53.4%)	10,725 (55.7%)
Area of residence					
Northeast Italy	59,521 (44.4%)	24,393 (52.1%)	14,775 (48.4%)	15,819 (42.2%)	4534 (23.6%)
Northwest Italy	18,531 (13.8%)	6658 (14.2%)	4310 (14.1%)	5747 (15.3%)	1816 (9.4%)
Central Italy	19,103 (14.3%)	5537 (11.8%)	4417 (14.5%)	5987 (16.0%)	3162 (16.4%)
Southern Italy	36,943 (27.5%)	10,235 (21.9%)	7040 (23.1%)	9936 (26.5%)	9732 (50.6%)
Birth cohort					
2004–2008	50,646 (37.8%)	17,769 (38.0%)	12,603 (41.3%)	12,351 (33.0%)	7923 (41.2%)
2009–2013	50,897 (38.0%)	17,203 (36.7%)	11,802 (38.6%)	14,317 (38.2%)	7575 (39.2%)
2014–2018	32,555 (24.2%)	11,851 (25.3%)	6137 (20.1%)	10,821 (28.8%)	3746 (19.4%)
Deprivation index quintile (missing = 18654)					
1st	22,295 (19.3%)	12,589 (31.6%)	8206 (31.0%)	9488 (29.2%)	3428 (20.7%)
2nd	23,604 (20.4%)	9371 (23.5%)	6450 (24.3%)	7493 (23.0%)	2982 (18.0%)
3rd	24,832 (21.5%)	7271 (18.3%)	5007 (18.9%)	6250 (19.2%)	3194 (19.3%)
4th	23,092 (20.0%)	5561 (14.0%)	3512 (13.3%)	4487 (13.8%)	2649 (16.0%)
5th	21,621 (18.8%)	5024 (12.6%)	3329 (12.6%)	4832 (14.8%)	4321 (26.0%)

All p-values (χ2 test) < 0.001

Table 4 Association between socio-demographic characteristics and antibiotic prescription trajectories

Membership to the antibiotic prescriptions trajectories vs. the "Very low use" trajectory (*n* = 115444)

	Group "low-to-moderate use" vs. "very low use" (2) vs. (1)		Group "moderate-to-low use" vs. "very low use" (3) vs. (1)		Group "high use" vs. "very low use" (4) vs. (1)	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Sex						
Males vs. females	1.08 (1.04–1.11)	1.07 (1.03–1.10)	1.20 (1.17–1.24)	1.20 (1.16–1.24)	1.37 (1.31–1.42)	1.35 (1.30–1.41)
Area of residence						
Northwest vs. Northeast	1.05 (0.72–1.52)	1.11 (0.74–1.67)	1.38 (0.89–2.15)	1.48 (0.91–2.40)	1.50 (0.68–3.29)	1.51 (0.67–3.35)
Center vs. Northeast	1.46 (0.99–2.15)	1.53 (1.01–2.34)	1.91 (1.20–3.03)	2.02 (1.22–3.35)	3.61 (1.59–8.18)	3.63 (1.58–8.35)
Southern vs. Northeast	1.28 (0.96–1.71)	1.36 (0.99–1.87)	1.60 (1.14–2.25)	1.65 (1.13–2.42)	4.71 (2.57–8.64)	4.84 (2.60–9.02)
Birth year						
2009–2013 vs. 2004–2008	0.97 (0.94–1.00.94.00)	0.95 (0.91–0.98)	1.21 (1.17–1.25)	1.20 (1.16–1.25)	0.94 (0.90–0.98)	0.94 (0.90–0.98)
2014–2018 vs. 2004–2008	0.73 (0.70–0.76)	0.70 (0.67–0.74)	1.31 (1.26–1.36)	1.28 (1.23–1.34)	0.59 (0.56–0.62)	0.58 (0.55–0.61)
Deprivation index quintile						
2nd vs. 1st	1.04 (0.98–1.09)	1.03 (0.98–1.09)	1.02 (0.97–1.08)	1.02 (0.97–1.08)	1.07 (1.00–1.14.00.14)	1.06 (0.99–1.14)
3rd vs. 1st	0.99 (0.94–1.04)	0.98 (0.93–1.04)	0.99 (0.94–1.04)	0.98 (0.94–1.04)	1.04 (0.97–1.11)	1.04 (0.97–1.11)
4th vs. 1st	1.02 (0.97–1.07)	1.01 (0.96–1.07)	1.00 (0.95–1.05)	1.00 (0.95–1.05)	1.03 (0.96–1.10)	1.02 (0.95–1.10)
5th vs. 1st	0.95 (0.90–1.01)	0.95 (0.90–1.00.90.00)	0.98 (0.93–1.03)	0.98 (0.93–1.03)	1.11 (1.03–1.19)	1.10 (1.02–1.18)

females and children born in Northeast Italy; the odds were lower for children born between 2009 and 2013 and 2014–2018 compared to those born between 2004 and 2008 (Table 4).

The odds of belonging to the "moderate-to-low use" vs. the "very low use" trajectory were higher for males and children residing in Central or Southern Italy compared to females and children living in Northeast Italy; they were also higher for children born between 2009 and 2013 and 2013–2018 compared to those born between 2004 and 2008.

Finally, the odds of belonging to the “high use” vs. the “very low use” trajectory group were higher for males and children residing in Central or Southern Italy compared to females and children living in Northeast Italy; in addition, the odds were lower for children born between 2009 and 2013 and 2014–2018 compared to those born in 2004–2008, and for children in the 5th ADI quintile compared to the 1 st (Table 4).

Discussion

In this study, we aimed to characterize patterns of antibiotic prescriptions in the first four years of life in primary care settings in Italy, using data from the Pedianet database. Among the 134,098 children included, a total of 684,010 antibiotic prescriptions were recorded during the study period. Children from Central and Southern Italy, as well as those born between 2004 and 2008, showed higher usage than children from Northern Italy and those born later.

We identified four distinct patterns of antibiotic use over the first four years of life, categorized as “very low use” (group [1]), “low-to-moderate use” (group [2]), “moderate-to-low use” (group [3]), and “high use” (group [4]).

Identified prescribing trajectories may reflect both distinct behavioral patterns of parents and FPs and, if considered as a proxy for bacterial infections, underlying differences in children’s health. Trajectory groups [1] and [2] represent optimal and desirable patterns of antibiotic prescription. Group [1] receives a low number of prescriptions during the first four years of life, potentially reflecting children whose parents seek care and receive prescriptions from the FP only for severely symptomatic infections, or children whose FPs strictly adhere to prescribing guidelines, limiting unnecessary prescriptions [34]. As a proxy for bacterial infections, these trajectories could also reflect healthy children, and/or children with good vaccination coverage [35]. Children in group [2] receive a higher number of prescriptions starting in the third and fourth years. This trend may reflect children with similar health characteristics and parental behavioral patterns to those in group [1]. When considered as proxy for infections, it likely reflects increased social exposure: in Italy, children aged three years and older typically begin interacting more with peers in educational settings such as kindergarten, with increased risk for infections [36].

Trajectory group [3] shows a peculiar pattern of prescription, with children receiving more antibiotics in their first two years of life than in the second two years of life. This pattern may reflect heightened medical attention during infancy [37], from both FPs and parents [38]. As proxy for infections, it may indicate early-life vulnerability to frequent infections, or chronic conditions increasing infections risk. Other possible explanations include the effect of early daycare attendance (before three years of age) or the presence of siblings in the family, both of which increase exposure to infections in early life [39]. We could further hypothesize that the decrease in the number of antibiotic prescriptions observed during the third and fourth years of life in these children could have been influenced by external factors, such as the COVID-19 pandemic, which has been associated in previous studies with immediate decreases in overall monthly antibiotic prescriptions for Italian children [21]. This suggestion is strengthened by the observation that children born between 2014 and 2018 were more likely to belong to this trajectory, and most of these children were three to four years old during the pandemic.

Trajectory group [4] includes children at greatest risk of developing adverse health outcomes due to excessive exposure to antibiotic prescriptions, that appears to be relevant since the newborn stage. This could underscore the presence of inappropriate prescription patterns, such as overprescription or use of antibiotics for mild or viral infections, as well as underlying health conditions predisposing to frequent infections [22].

Among the determinants investigated in shaping pediatric antibiotic use in this Pedianet cohort, we included geographical and temporal characteristics. The findings from the current study reveal that children residing in Central and Southern Italy had a higher likelihood of being in the trajectory groups with higher exposure to antibiotic prescriptions. The presence of relevant differences in antibiotics prescriptions between Northern and Southern Italy has been already identified in recent studies [40, 41] as well as in the 2021 and 2023 National Report on antibiotic use [23, 42] and in related publications [43]. These differences may be linked to variability in parental social and economic factors, that we described using deprivation index as a proxy, which strongly influence healthcare-seeking behavior and parental knowledge of correct antibiotic use in children, being included among well-known determinants of child health inequalities [38, 40]. Available evidence also shows that healthcare providers are more inclined to prescribe antibiotics to patients from deprived backgrounds, due to concerns about complications and pressure [44]. A potential role of differences in infection occurrence between Italian areas appears unlikely, and if such differences exist, the milder climate would likely favor Southern Italy, which, instead, is the area with the highest antibiotic use.

Fortunately, we assessed that children more recently born were less likely to be included in the second or fourth trajectory group, while children born earlier were more likely to be assigned to group [4]. This result may be attributed to the positive effects of educational campaigns conducted in Italy in the last years to promote a more appropriate antibiotic use among children, such as the National Action Plan on Antimicrobial Resistance (PNCAR) [45].

With regard to the choice of antibiotics, we observed that penicillins constitute the majority of prescriptions. Still, cephalosporins and macrolides also play a significant role, accounting for 43% of prescriptions. According to the AWaRe classification (Access, Watch, Reserve) implemented by the World Health Organization [46], some of the molecules pertaining to the cephalosporin and macrolides classes should be included in the “Watch” group and should therefore be used only for specific and limited infections, as they show great potential to induce antibiotic resistance. Our findings align with those provided by Barbieri and colleagues, who focused on antibiotic prescription patterns observed from 2012 to 2018 and from 2019 to 2021 in Italy. They underlined the significant number of prescriptions for broad-spectrum antibiotics, which persisted even after containment measures adopted during the pandemic [20, 21].Some limitations need to be addressed in this study. Firstly, we considered antibiotic prescriptions as a proxy for antibiotic use and it was impossible to gather information with respect to antibiotic prescriptions received outside the primary care setting. Additionally, we were unable to retrieve information regarding the indications for which antibiotics were prescribed. However, it seems unlikely that their high use in some of the identified groups was always appropriate and necessary, and recent studies already highlighted the presence of inappropriate prescribing behaviors in the pediatric population in Italy [21]. Other limitations relate to the source of information used. The exclusive reliance on Pedianet data limits the generalizability of our findings to children not followed by FPs participating in the Pedianet network and to contexts outside primary care, potentially introducing selection bias. Generalizability is further restricted by the exclusion of children with incomplete follow-up or those born preterm. Additionally, because children born up to 2018 were included, our observation period encompassed the COVID-19 pandemic. The unique circumstances of lockdowns and reduced social contact may have introduced bias across all identified trajectories, not only in trajectory group [3]; these factors could have led to an underestimation of the overall magnitude of antibiotic use in the Italian pediatric population. While the identified trajectories provide valuable insights into pediatric antibiotic use in Italian primary case settings, caution is needed when applying these findings to children not included in the Pedianet network, in other healthcare settings, or in different temporal contexts.

Although GBTM has been increasingly used, especially in recent years, to describe patterns of medication use and adherence in other clinical contexts [47–49], its application to antibiotic prescribing patterns, to our knowledge, remains limited. The use of GBTM in this study provides substantial methodological advantages, as it captures unobserved heterogeneity in data, and allows for a more nuanced understanding of prescribing dynamics in early childhood. By identifying distinct trajectories, we were also able to explore how different determinants influence children’s likelihood of belonging to specific antibiotic use patterns. Moreover, GBTM offers a visually intuitive representation of temporal patterns of antibiotic exposure, facilitating interpretation and communication of findings.

Conclusion

Despite recent findings highlighting an overall decrease in antibiotic prescriptions over the last years, Italian children are still highly exposed to them in their first years of life, potentially leading to negative health consequences.

The results obtained with GBTM techniques have served as a starting point for observing longitudinal changes in prescription patterns over the last 20 years, providing a clear picture of how prescribing behaviors evolved in the Italian pediatric population included in Pedianet. By identifying distinct trajectories of prescription, we were able to better understand the influence of sociodemographic and geographical determinants. The visual representation of these trajectories could also be utilized in the future to evaluate the effectiveness of antibiotic stewardship interventions in the Italian primary care setting, and to support targeted strategies for populations at higher risk of excessive prescribing.

Abbreviations

FP	Family pediatrician
GBTM	Group-based Trajectory Modelling
ADI	Area deprivation index
ATC classification	Anatomical Therapeutic Chemical classification
BIC	Bayesian Information Criterion
OR	Odds ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-25657-x.

Supplementary Material 1. Figure S1: flowchart for children’s inclusion in the study (n=134098). Table S1: Number of subjects with at least one antibiotic prescription in the periods of reference. Table S2: Number of children with at least one antibiotic prescription in the trimesters considered for GBTM. Table S3: Model comparison indices for combinations of polynomial functions with different shapes for the 4 trajectory groups identified by GBTM.

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Authors' contributions
AC and CC designed the study and were responsible for funding acquisition. GP, EB and IR analyzed the data; DD and IR drafted the manuscript; AC, CC and CG reviewed and commented on various versions of the manuscript. All authors provided approval of the final manuscript and agreed to be accountable for all aspects of the work.

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Data availability
The data underlying this article are not publicly available. Deidentified data could be shared upon reasonable request to the corresponding author and approval of the Internal Scientific Committee of Società Servizi Telematici Srl, the legal owner of Pedianet.

Declarations

Ethics approval and consent to participate
This is an observational, retrospective, noninterventional study. According to a bylaw on the classification and implementation of observational drug-related research, as issued by the Italian National Drug Agency (an entity belonging to the Italian Ministry of Health), this study does not require approval by an ethics committee in Italy (Italian Drug Agency note on August 3, 2007). This study was conducted in accordance with the tenets of the Declaration of Helsinki and was compliant with the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance's Guide on Methodological Standards in Pharmacoepidemiology. The Internal Scientific Committee of Società Servizi Telematici Srl, the legal owner of Pedianet, approved ethical approval of the study and access to the database.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Unit of Biostatistics, Epidemiology and Public Health, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Padua, Italy
[2]Division of Biostatistics, Epidemiology and Public Health, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy
[3]Department of Women's and Children's Health, University of Padua, Padua, Italy
[4]Division of Pediatric Infectious Diseases, Department for Women's and Children's Health, University of Padua, Padua, Italy

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