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ORIGINAL ARTICLE

Reducing antibiotic prescriptions in children is not associated with higher rate of complications

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Abstract

Acute otitis media (AOM) and sore throat are common reasons for antibiotic prescription in children. Starting from 2007, evidence-based guidelines and other multifaceted improvement activities (ProBA project) were implemented in Emilia-Romagna, a northern Italian region. Antibiotic prescription rate in the region decreased with time (37% relative reduction from 2005 to 2019). Within the ProBA project, this retrospective observational study, including all hospitals of the region, aims to assess if lower rate of antibiotic prescription was associated with an increased rate of acute mastoiditis and acute rheumatic fever (ARF). Hospital admission rates for acute mastoiditis and ARF from 2005 to 2019 were calculated using ICD-9 codes. Hospital intervention rates for myringotomy, incision of mastoid, and mastoidectomy were also assessed. A comparison with antibiotic prescription rate in the pediatric population was performed. Data were gathered using administrative databases and trends were calculated using Poisson regression. During the study period, rate of mastoiditis and similar diagnosis declined from 54.1 to 33.6 per 100.000 (β coefficient = − 0.047, p value < 0.001) and rate of surgical treatment from 134.6 to 89.6 per 100.000 (β coefficient = − 0.036, p value < 0.001), whereas rate of ARF remained stable at around 4.4–4.8 per 100.000 (β coefficient = − 0.009, p value = 0.472).

Conclusion: ProBA project implementation—recommending 5 days of amoxicillin for AOM when needed and 6 days of amoxicillin when streptococcal pharyngitis is detected—was associated with a reduced antibiotic use without an increase of complications.

What is Known:
- *Acute otitis media (AOM) and streptococcal pharyngitis are common pediatric infections and frequent cause of antibiotics prescription.*
- *Fear of rare complications like mastoiditis and acute rheumatic fever can hinder health professionals' compliance with evidence-based guideline.*

What is New:
- *Guidelines recommending a short course of antibiotics for AOM and streptococcal pharyngitis are associated with reduced antibiotic prescriptions and no increase of complications.*
- *Analysis based on administrative databases is useful for monitoring projects and supporting health professionals in complying with guidelines.*

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Abbreviations

AOM	Acute otitis media
ARF	Acute rheumatic fever
CDC	Centers for Disease Control and Prevention
DRG	Diagnosis-related group
ECDC	European Centre for Disease Prevention and Control
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICD-9	International Statistical Classification of Diseases and Related Health Problems-ninth revision
ProBA project	[Progetto Bambini e Antibiotici] Children and Antibiotics Project
WHO	World Health Organization

Introduction

Acute otitis media (AOM) and sore throat are among the most common reasons for ambulatory visit and antibiotic prescription in pediatric primary care in high-income countries [1].

Emilia-Romagna is a large Italian region with about 4.5 million inhabitants, with a regional public health system characterized by a long tradition of data monitoring and audit for improvement project, also in the field of antibiotic appropriateness. Within this context, the ProBA project (Progetto Bambini e Antibiotici), a long-lasting multilevel intervention aimed at promoting appropriate use of antibiotics in children, was started in 2005 [2]. Guidelines on AOM and sore throat in children were developed in 2007 (ProBA phase 1) and updated in 2015 (ProBA phase 2); recommendations were implemented with the support of primary care and hospital pediatricians. For AOM, implementation of a wait-and-see strategy (or safety-net antibiotic prescriptions) and use of amoxicillin during 5 days when needed was recommended; for sore throat, diagnosis using Mc Isaac score plus rapid antigen test when appropriate and 6 days of treatment with amoxicillin for streptococcal cases were the main recommendations [2]. Antibiotic prescription rate in children decreased from 1307 per 1000 children in 2005, before the ProBA project was launched, to 822 per 1000 children in 2019 (37% relative reduction); an increase in the use of first-line antibiotic (amoxicillin) and a reduction of second-line antibiotic (amoxicillin plus clavulanic acid) were also detected [3].

Two reports, one of an increase of acute mastoiditis, a complication of AOM [4], and the other one of acute rheumatic fever (ARF) with carditis, a rare complication of streptococcal pharyngitis [5], have been published since, referring to data gathered in a single university hospital. Data presented could not be used to infer an association between short course of antibiotics and complications detected [6] but suggested the need to monitor the trend of acute mastoiditis and ARF incidence. The aim of this study was to monitor incidence of acute mastoiditis and ARF in children living in the Emilia-Romagna region, starting from 2005 (before the ProBA project was implemented) to detect if an increase of these complications actually occurred along with ProBA implementation and concurrent antibiotic prescription reduction.

Methods

We conducted a population-based observational study including all children (age 0–13 years) resident in the Emilia-Romagna region during the study period (from 2005 to 2019). Primary outcomes were hospital admission rate for acute mastoiditis and hospital admission rate for ARF in the study population, all hospitals within the region being included. Anonymized patient-level data were gathered from the hospital administrative system. Cases were included if identified diagnosis-related group (DRG) codes at discharge of acute mastoiditis or ARF, according to the International Statistical Classification of Diseases and Related Health Problems (ICD)-9 (annex 1 in the supplementary material), were retrieved in primary or secondary diagnosis.

As acute mastoiditis is not a clear cut diagnosis [7, 8], and professional attitude or setting of care can impact on code assignment [9], hospital admission rates for conditions that can be considered in a differential diagnosis for acute mastoiditis like external acute otitis, acute otitis media, effusive otitis media DRG codes used reported in annex 1 in the supplementary material) were also assessed. Moreover, data on surgical intervention typically related to acute mastoiditis management and treatment (myringotomy, incision of mastoid, and mastoidectomy) were collected.

Data on ARF included pediatric cases with and without cardiac involvement (DRG codes used reported in annex 1 in the supplementary material).

Data were gathered retrospectively; in the case of repeated admission for rheumatic fever in the same subject, only first admission was counted. Repeated hospital admission for acute mastoiditis or similar diagnosis occurring within 4 weeks was considered residual mastoiditis and counted as one case; recurrence after 4 weeks was counted as a new episode [9].

Analysis was done based on child sex, age group, and nationality (Italian versus not Italian).

Statistical analysis was carried out using the Stata statistical software package version 14.2. Trends were calculated using Poisson regression.

Results

Acute mastoiditis

From 2005 to 2019, there were 1181 children discharged with a primary or secondary diagnosis of acute mastoiditis; in 1042 cases, (88.2%) acute mastoiditis was the primary diagnosis. Cases were largely males (60.9%) and Italians (88.6%); from 2005 to 2019, the median age at hospital admission increased from 2.5 to 4.0 years, and the mean age from 3.6 years to 5.0 years (Table 1).

In the same period, there were 1858 children discharged with a primary or secondary diagnosis of otitis (external acute otitis, AOM, effusive otitis media); in 669 cases (36.0%), otitis was the primary diagnosis. Cases were largely males (58.0%) and Italians (83.3%); the median age (2 years) and mean age (2.9 years) at hospital admission remained substantially stable during the study period (Table 1).

Acute mastoiditis hospital admission showed an irregular increasing trend during the study period that reached a statistical significance: from 58 cases (rate 12.2 per 100.000) to 115 cases (rate 21.1 per 100.000) (β coefficient = 0.020, p value = 0.004), whereas in the same period, otitis hospital admission (AOM, external acute otitis, and effusive otitis media) decreased: from 200 cases (rate 41.9 per 100.000) in 2005 to 68 cases (rate 12.5 per 100.000) in 2019 (β coefficient = − 0.091, p value < 0.001). As some overlapping is possible between the two conditions, total hospital admission rate for otitis and mastoiditis was calculated and reported together: overall rate was 54.1 per 100.000 in 2005 and decreased to 33.6 per 100.000 in 2019, with a trend statistically significant (β coefficient = − 0.047, p value < 0.001) (Fig. 1).

Surgical interventions typically associated with acute mastoiditis, i.e., myringotomy, incision, and drainage of the mastoid, and mastoidectomy declined from 642 interventions (rate 134.6 per 100.000) to 488 (rate 89.6 per 100.000); the reduction was statistically significant (β coefficient = − 0.036, p value < 0.001). Rates of surgical interventions related to acute mastoiditis are reported in Fig. 2: a pattern in reduction is detected irrespective of the reported number of mastoiditis hospital admissions.

Acute rheumatic fever

From 2005 to 2019, there were 375 children discharged with a primary or secondary diagnosis of ARF (194 cases with cardiac involvement and 181 without cardiac involvement); in 332 cases (88.5%), ARF was the primary diagnosis. Cases were largely males (58.1%) and Italians (89.1%) (Table 1). Median age at hospital admission was 8.0 years (mean 8.3 years), without significant modification during the study period (Table 1). ARF hospital admission remained largely stable during the study period (around twenty cases per year overall) with a single peak in 2013 with 41 cases. ARF overall rate decreased slightly, without reaching statistical significance (4.8 per 100.000 in 2005 and 4.4 per 100.000 in 2019; β coefficient = − 0.009, p value = 0.472), ARF with cardiac involvement increased, but the increase was not statistically significant (1.5 per 100.000 and 2.9 per 100.000; β coefficient = 0.024, p value = 0.159), whereas ARF without cardiac involvement rate decreased with time and the reduction was statistically significant (3.4 per 100.000 and 1.5 per 100.000; β coefficient = − 0.044, p value = 0.013) (Fig. 3).

Discussion

Based on regional administrative data of hospital discharge, pediatric (0–13 years) rate of acute mastoiditis and similar diagnosis and ARF, with and without cardiac involvement, remained stable or even decreased during the study period (2005–2019), along with ProBA project implementation.

ProBA guidelines for AOM and for sore throat in children, developed using the GRADE methodology [10], and based on local antimicrobial resistance data [11, 12], were firstly issued in 2007 and thereafter updated in 2015 [2]. A gradual and significant reduction of antibiotic prescription in the pediatric population was observed, starting from 2009; a slight reversion of the trend has been observed in the last 2 years, but these fluctuations were not associated with increased rate of AOM complications or streptococcal pharyngitis complications.

Acute mastoiditis rate showed some fluctuation with an increasing trend during the study period. At the same time, a clear reduction in hospital admission due to other conditions that can resemble acute mastoiditis (acute otitis media, external acute otitis, and effusive otitis media) was detected, as well as an overall reduction of surgical intervention for mastoiditis, both in the pediatric population overall and in the pediatric population with discharge diagnosis of acute mastoiditis. According to these results, it is not possible to rule out a growing trend to use the ICD-9 codes of mastoiditis in doubtful cases which could have led to a misclassification of a part of the cases of otitis into mastoiditis. This hypothesis is supported by the fact that the apparent increase in mastoiditis is associated with a decrease in surgical procedures for the treatment of this condition in more recent years. This explanation is consistent with other experiences [7–9] that point toward an overdiagnosis of mastoiditis and misclassification with various form of otitis: in particular, in Sweden [9], a retrospective re-evaluation of 1966 records of patients with ICD9 codes of mastoiditis or otitis showed that out of 529 records with a

Table 1 Hospital admission due to mastoiditis, otitis, acute rheumatic fever, number of cases, sex, nationality, and patient age (2005–2019)

Year of hospital admission	Mastoiditis					Otitis					Acute rheumatic fever				
	Number	Sex (% male)	Nationality (% IT)	Age		Number	Sex (% male)	Nationality (% IT)	Age		Number	Sex (% male)	Nationality (% IT)	Age	
				Mean (years)	Median (years)				Mean (years)	Median (years)				Mean (years)	Median (years)
2005	58	58.6	91.4	3.6	2.5	200	57.0	87.0	2.7	2	23	69.6	91.3	8.5	9
2006	75	57.3	90.7	4.2	3	179	56.4	88.8	2.6	2	31	51.6	96.8	8.2	8
2007	73	68.5	91.8	3.9	3	140	64.3	87.9	3.0	3	19	52.6	89.5	8.5	9
2008	62	61.3	88.7	4.1	3	161	57.1	81.4	2.9	2	20	50.0	95.0	7.6	7
2009	76	55.3	86.8	4.1	3	163	57.1	87.1	3.0	2	29	69.0	93.1	7.6	8
2010	74	71.6	82.4	3.4	2.5	139	59.0	79.1	2.9	2	22	45.5	86.4	8.0	8
2011	73	63.0	91.8	3.7	3	169	53.8	83.4	3.0	2	25	48.0	96.0	7.8	8
2012	69	71.0	94.2	4.8	4	139	70.5	81.3	2.8	2	26	73.1	92.3	9.2	10
2013	84	60.7	85.7	4.4	4	109	60.6	76.1	2.8	2	41	85.4	90.2	9.1	9
2014	81	50.6	86.4	4.0	3	98	54.1	83.7	3.2	2.5	22	54.5	77.3	8.7	9
2015	104	59.6	90.4	5.2	4	89	59.6	85.4	3.6	3	16	31.3	81.3	7.2	7
2016	72	50.0	88.9	5.1	4.5	58	46.6	77.6	3.7	2.5	25	56.0	76.0	8.5	9
2017	91	59.3	82.4	5.0	4	71	62.0	78.9	3.5	3	28	60.7	96.4	8.1	7
2018	74	68.9	91.9	5.8	5	75	40.0	78.7	2.6	1	24	45.8	87.5	7.5	7.5
2019	115	60.0	87.8	5.0	4	68	64.7	79.4	2.4	1	24	45.8	79.2	9.2	9
Overall	1181	60.9	88.6	4.5	4	1858	58.0	83.3	2.9	2	375	58.1	89.1	8.3	8

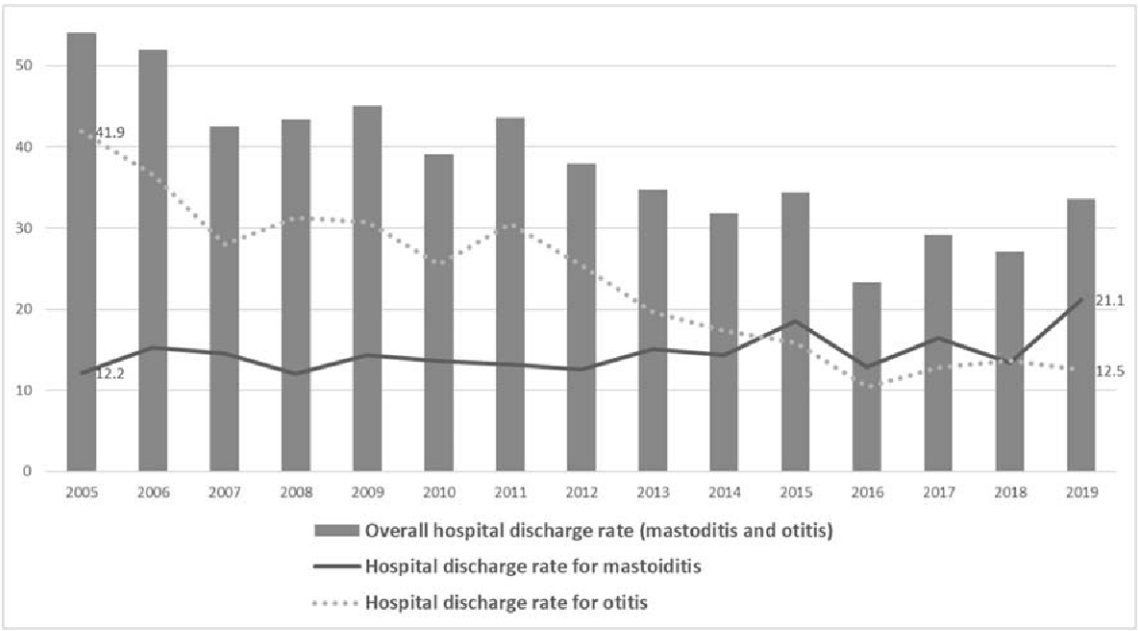

Fig. 1 Hospital discharge rate for mastoiditis, otitis, and overall (2005–2019)

discharge code of acute mastoiditis, only 75% of the patients did have a correct diagnosis of mastoiditis, the remaining being various forms of otitis. Similarly, ARF, both with and without cardiac involvement, did not increase during the study period. Fluctuations occurred, with a single peak occurring in 2013, without any correlation with antibiotic prescription rate. Episodic clusters of ARF are known to occur due to periodical circulation of more rheumatogenic strains of beta-hemolytic group A streptococcus or among group of disadvantaged people [13]. The slight increase in ARF with cardiac involvement detected, though not statistically significant, can be associated with an increased detection of subclinical cardiac involvement through ultrasound assessment: criteria for defining cardiac involvement in ARF episodes changed in 2015 [14]. However, the reduction in the overall rate of ARF observed during the study period is reassuring.

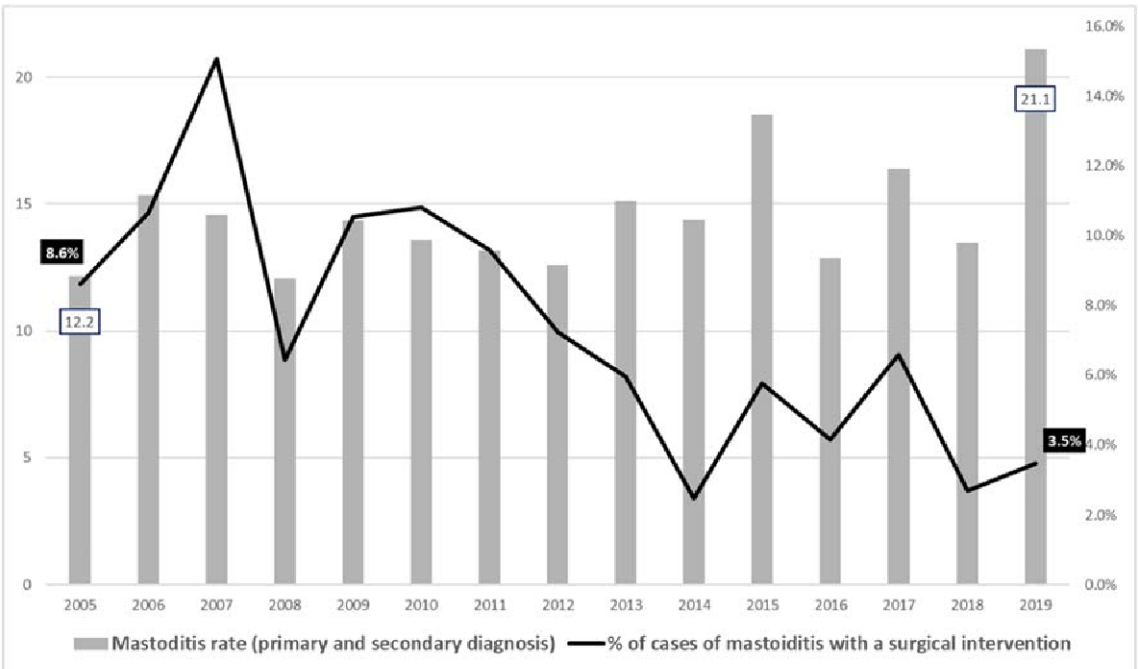

Fig. 2 Rate of mastoiditis and percentage of cases needing a surgical intervention (2005–2019)

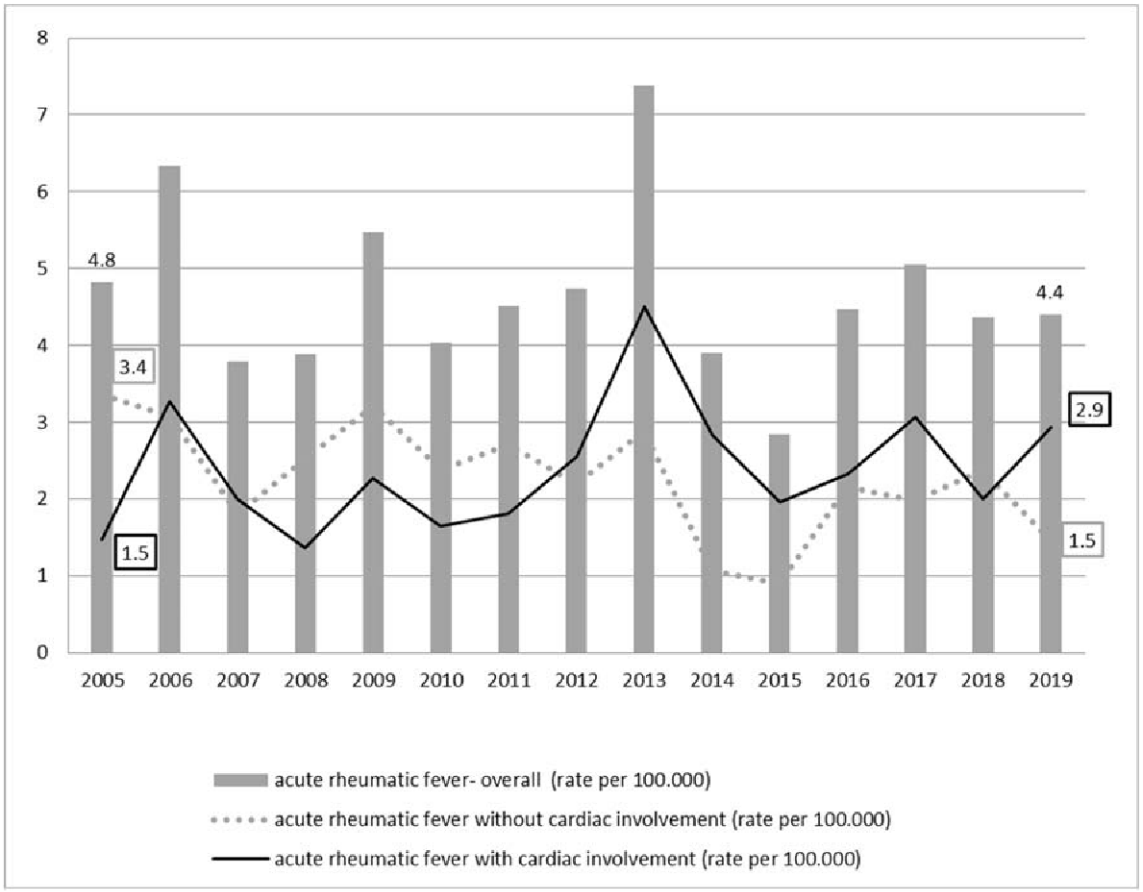

Fig. 3 Rate of ARF, with and without cardiac involvement and overall (2005–2019)

One interesting aspect to be analyzed is the over-representation of children of Italian nationality in the study population: hospital admission for acute mastoiditis and ARF involved more often Italian children, rates of Italians admitted being respectively 88.6% and 89.1%, whereas overall, in the Emilia-Romagna region, the rate of Italians in the age group 0–13 years is 78.9%. Differences in health-seeking behavior between parents of Italian and not Italian children, or different professional attitudes, can influence this over-representation of Italian children admitted, which warrants further analysis.

Strength of this study is completeness of data, with hospital discharge codes retrieved from all hospitals within our regional area: conclusions are therefore valid with respect to our pediatric population and can be valid for other contexts similar to the one here described. Our regional hospital system is characterized by a high retention rate and even an attraction rate for patient from adjacent regions; moreover, it is uncommon for families to look for extra-regional hospital care specifically for acute respiratory infection. Therefore, we can be confident that all children with acute mastoiditis or ARF during the study period have been included in our study. Moreover, the long time period of surveillance, encompassing the beginning of the ProBA project, allows us to analyze jointly trend of hospital admission rate for acute mastoiditis and ARF and antibiotic prescription rate trend from 2005 to 2019, providing robust evidence of temporal trend.

A study limitation is that only discharge codes were used to identify hospital discharge diagnosis: it is well known that acute mastoiditis and ARF estimates exclusively based on hospital discharge codes assessment provide inflated rates [9, 15]. However, in this case, bias would be in the excess side; therefore, our conclusion that a reduction of antibiotic prescription rate is not associated with an increase rate of complications of AOM and of streptococcal pharyngitis is eventually reinforced. Another limitation is that we do not know the reasons for antibiotic prescriptions, as the Italian prescription system does not register diagnosis. Thus, it is not possible to link antibiotic prescription to single AOM or acute pharyngitis episodes. However, a similar study design has been previously applied providing sensible information [16].

Our experience is consistent with other ones already described: high-income countries with antibiotic prescription rate lower than our and using recommendation for common respiratory infections similar to the ones issued within the ProBA project have not experienced an increased risk of ARF [16], mastoiditis [16–19], or other bacterial complication [20, 21].

Italy overall is a country with a high antibiotic prescription rate [22]. Extending the Emilia-Romagna experience with the ProBA project to the rest of the country could make an impact toward a more appropriate use of antibiotic in the pediatric population at national level. Similarly, there are other high-income countries with low compliance to evidence-based recommendation for common pediatric infections that could benefit from applying a multifaceted intervention for quality improvement similar to ProBA: a recent experience showed that in English primary care, there is a critical over-prescription of antibiotics for common acute respiratory infections [23]. Finally, even in Emilia-Romagna, prescription rates are still high compared with other countries [24], and further improvement are needed [25] to reduce antibiotic resistance and to protect health in children and in the general population, as advocated by the World Health Organization (WHO) [26], the European Centre for Disease Prevention and Control (ECDC) [27], and the Centers for Disease Control and Prevention (CDC) [28].

In conclusion, implementation of recommendation similar to the ones included in the ProBA guidelines for AOM and sore throat, opportunely adapted based on local patterns of antimicrobial resistance [11, 12], should be more widely pursued in high-income countries, as well as monitoring of antibiotic prescription in children, acute mastoiditis, and ARF rates. This set of activities is likely to produce an increased appropriate use of antimicrobials and a reduction of antimicrobial resistance; at the same time, it provides useful information to health policy-makers and can be of reassurance for health professionals and the families.

Authors' contribution SDM: study conceptualization and design, drafting the first version of the manuscript, reviewing and editing of the final version of the manuscript, online submission

CG: study design, data curation and analysis, reviewing and editing of the final version of the manuscript

RB: study methodology, data curation, reviewing the final version of the manuscript

MF: study supervision, clinical insights, reviewing the final version of the manuscript

ID: study supervision, clinical insights, reviewing the final version of the manuscript

LB: study supervision, human resources allocation, reviewing the final version of the manuscript

MLM: study supervision, human resources allocation, reviewing the final version of the manuscript

All co-authors approved the final version of the manuscript.

Compliance with ethical standards

Competing interests The authors declare that they have no conflict of interest.

Ethics approval and consent to participate N/A

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