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Evaluating academic detailing as an antibiotic stewardship intervention in primary healthcare settings in Croatia

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Abstract

Background Acute respiratory tract infections are common in primary healthcare care settings and frequently result in antibiotic prescriptions, despite being primarily viral. There is scarcity of research examining impact of academic detailing (AD) intervention on prescribing practices for these infections in resource-constrained healthcare settings like southeastern Europe. Therefore aim of this study was to evaluate impact of AD intervention as an antimicrobial stewardship measure on antibiotic prescribing for acute respiratory tract infections in primary setting in Croatia which is located in southeastern Europe. Secondary goal included examining incidence of *Clostridioides difficile* infections (CDI) which are often associated with antibiotic consumption.

Methods AD intervention was implemented from 1st to 30th April 2020 and led by hospital healthcare professionals (infectious disease physician, clinical microbiology physician and clinical pharmacist). They focused on enhancing prescribing behaviors of primary care physicians (PCPs) by presenting local data, supplemented by examples from everyday practice, research and guidelines highlighting negative consequences of imprudent antibiotic use. This feasibility quasi-experimental study had two control groups in two counties. Impact of AD intervention was assessed by analyzing antibiotic prescription patterns using log-linear model, adjusting for seasonality. Study focused on prescribed daily defined doses (DDD) per day among PCPs pre-intervention (from 01st January 2018 to 31st March 2020) and post-intervention (from 1st May 2020 to 31st December 2022).

Results Data was collected from sixteen out of fifty-seven eligible PCPs with mean 29 years (SD 11.38) in practice. Statistically significant difference results ($p < 0.05$) favored AD intervention, leading to 30% decline in antibiotic prescribing in adjusted DDD per day for acute pharyngitis (21.14 post-intervention/30.27 pre-intervention), 33% decline for acute tonsilitis (24.91/37.38), 23% decline for acute upper respiratory infection (21.26/27.62) and 36% decline for acute bronchitis (8.13/12.77). Although there was 14% decline for acute sinusitis post-intervention, it did not reach statistical significance (30.96/35.93) ($p = 0.617$). Incidence of CDI cases decreased in investigated county while in control county stayed the same. Inter-county difference in these changes was not statistically significant (ratio = 0.749, 95% CI, 0.460–1.220; $p = 0.246$).

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Conclusions This feasibility study showed reductions in antibiotic prescribing for acute respiratory tract infections, emphasizing the efficacy of targeted, educator-led programs. Tailored healthcare strategies are vital, especially in Croatia and southeastern Europe, for promoting sustainable practices and addressing antimicrobial resistance challenges.

Keywords Antimicrobial resistance, Antibiotic prescribing, Primary care, Acute respiratory tract infections, Antimicrobial stewardship, Academic detailing, Feasibility study

Introduction

Antibiotics, considered essential in a modern medicine, face an increasing risk of diminished effectiveness due to overuse, antimicrobial resistance (AMR) and the lack of new discoveries since the 1970s [1]. Primary care physicians (PCPs) contribute to this problem by frequently overprescribing antibiotics, particularly for viral acute upper respiratory tract infections (ARI) and acute bronchitis (AB), with up to 50% of these prescriptions being unnecessary [2–7]. This is alarming, as over 90% of overall antibiotic prescriptions in European Union Member States (EU) and European Economic Area (EEA) countries occur in primary health care [2]. All prescribing can lead to medication-related adverse events and antibiotic prescribing also contributes to the rising incidence of community cases of *Clostridioides difficile (C.diff.)* infection [8–10]. However, the most alarming problem is the rising emergence and spread of drug-resistant bacteria, leading to AMR infections, which threatens our ability to treat common infections [11, 12]. AMR occurs when bacteria change due to being exposed to antimicrobial drugs and no longer respond to these drugs. In 2019, AMR ranked as the third leading cause of death with only ischaemic heart disease and stroke accounting for more deaths [13]. Addressing this AMR challenge requires more innovative measures, especially for southeastern European countries, where the AMR burden is over 40% higher per 100,000 inhabitants compared to western Europe [14–16]. In this region, overall antibiotic consumption across all types and indications is notably two to three times higher than in Western Europe, underscoring the strong correlation between antibiotic use and increased AMR [2, 17]. Consequently, the implementation of comprehensive antimicrobial stewardship programs (ASPs) is highly recommended to effectively address this important issue.

ASP foster prudent antibiotic use and aim to improve patient outcomes, slow resistance, prevent death from resistant infections, and reduce healthcare costs [18–20]. A typical antimicrobial stewardship team (A-team) mostly includes an infectious disease physician, a clinical microbiology physician and a clinical pharmacist [14, 15, 20, 21]. Promising approaches of ASPs to reduce the unnecessary antibiotic treatment in ARIs and ABs are audit feedback with peer comparison, academic detailing (AD), and clinician communication training [22–24]. AD involves one-on-one meetings, where peers, colleagues, or clinicians present evidence-based information aimed at modifying antibiotic prescribing practices. This approach is considered both low-cost and well-received [25–27]. For example, a significant 41% reduction in unnecessary use of targeted antibiotics was achieved through AD intervention in US hospitals [28]. However, Norwegian and Irish primary care studies have shown limited impact on ARI antibiotic prescribing, highlighting several key challenges inherent in influencing antibiotic usage in primary care settings [29, 30]. These challenges include: patient demand and expectations for antibiotics or PCPs anxiety about potential deterioration in a patient's condition if antibiotics are not prescribed [30].

Currently, there is a scarcity of research on AD in resource-constrained healthcare settings, particularly during the COVID-19 pandemic, which may influenced prescribing practices for ARIs and AB [31, 32]. This gap underscores the need to explore the effectiveness and adaptability of AD interventions during health crises. Implementing feasibility studies on AD strategies is vital for advancing health services in today's dynamic, resource-limited healthcare environment, where evidence-based approaches and implementation science play a role in optimizing investments and public health outcomes [33, 34]. Furthermore, the applicability of AD for promoting prudent antibiotic use in ARIs and AB, particularly in southeastern Europe, lacks detailed research. Unlike in Northern and Western Europe, most healthcare institutions in southeastern Europe do not have established ASPs, despite their demonstrated benefits in rationalizing antibiotic use, as shown in Croatia [35]. This region faces significant healthcare resource constraints, including limited implementation of ASPs, shortage of dedicated personnel, insufficient diagnostic capabilities, and limited funding for stewardship initiatives. AD could potentially impact this area as a cost-effective intervention requiring minimal resources, an educational tool for healthcare providers, an adaptable approach tailored to region-specific challenges, and a stepping stone towards more comprehensive stewardship efforts. Therefore, the primary aim of our study was to evaluate the impact of an AD intervention as ASP on

PCPs' antibiotic prescribing for acute respiratory tract infections (ARIs and AB) in Croatia. The secondary aim included examining the incidence of *C.diff.* infections (CDI) potentially linked to antibiotic usage, where a reduction in incidence could signify an additional benefit of AD.

Methods

This study was conducted across two distinct Croatian counties. In the first county, Koprivnica-Križevci County (KKC) with a population of 101 661 and 57 PCPs [36], we established both intervention and control groups to assess the direct effects of the AD intervention. The second county, Bjelovar-Bilogora County (BBC) with a population of 102 295 and 67 PCPs [36], was designated as an additional control group, providing a comparative baseline to further validate the impact of the AD intervention.

Population and procedure enrolment

A quasi-experimental feasibility study with two control groups, was conducted to evaluate improvements in antibiotic prescribing within a primary health care setting. Study focused on AD intervention group in KKC situated in northern Croatia. AD intervention was implemented from 1st to 30th April 2020. We attempted to recruit all fifty-seven PCPs listed by the Croatian Health Insurance Fund in KKC, though not all were ultimately enrolled in the study. The first control group comprised non-participating KKC PCPs. The second group included sixty-seven PCPs in neighbouring BBC, which had a similar population and comparable medical practices. Study focused on pre-intervention (from 01st January 2018 to 31st March 2020) and post-intervention (from 1st May 2020 to 31st December 2022) period, coinciding with the COVID-19 pandemic.

PCPs in KKC were recruited through local workshops held in Koprivnica, Križevci, and Đurđevac, from September to November 2019 with similar objectives as AD intervention [37]. The same A-team performed workshops and AD intervention. Participants earned continuous medical education points with no compensation provided. Efforts, supported by KKC, included local press conferences, press releases, and radio podcasts to raise awareness, promote prudent antibiotic use, and discourage patient pressure on PCPs [38, 39]. They also received educational materials such as posters for PCPs' practices and patient-friendly brochures. PCPs in BBC did not receive any of these interventions.

Ethical approval

The research underwent review and approval by the Regional Committee for Medical and Health Research Ethics for Outpatient Clinics of Koprivnica-Križevci County (reference number 2137–16–5266/2021). All participants provided informed consent. Additionally, we obtained ethical approval for data collection from Croatian Institute of Public Health (reference numbers 030–02/23–15/8 and 117–15–23–2), and informed consent was secured from all identified PCPs in KKC and BBC. No personal data of PCPs or patients were included. We identified prescriptions for patients diagnosed with ARI and AB linking them to PCPs using unique identifiers. Furthermore, adhering to STROBE-AMS guidelines, the study aimed to enhance reporting on the link between AMR and antibiotic use, contributing to ASP improvements [40, 41].

Academic detailing intervention

A hospital health-care A-team in KKC, comprised of an infectious disease physician, a clinical microbiology physician, and a clinical pharmacist, led the one-time 30-min AD intervention. This was an educational in-person presentation delivered to individual PCP who agreed to participate. The setting was PCP's own medical practice, providing a familiar and comfortable environment for learning.

The in-person materials covered a comprehensive range of topics related to antibiotic use and ASP (supplement 1):

1. Overview of antibiotic consumption in Croatia and comparison with neighbouring countries
2. Differences between community and hospital antibiotic consumption
3. Consequences of AMR
4. Most frequently prescribed antibiotics by diagnosis, based on literature and local data
5. Definition and goals of ASP
6. Practical implications of ASP from microbiology, infectiology, and clinical pharmacy perspectives
7. Update on national guidelines for self-limited respiratory infections, sore throat and acute sinusitis
8. Negative consequences of antimicrobials (side effects, allergic reactions), with emphasis on those commonly prescribed for ARIs
9. Reminder where to find current national and international guidelines
10. A-Team Strategies and key messages
11. Reminder with important questions when prescribing antibiotics
12. Sharing posters for PCPs' practices and patient-friendly brochures emphasizing prudent antibiotic use.

This comprehensive approach provided attendees with both a broad understanding of ASP and specific, practical knowledge applicable to primary care settings.

The A-team's interaction with outpatient care and PCPs differs significantly from their hospital-based interventions. In the outpatient setting, the A-team concentrates on education, guideline dissemination, and offering support for complex cases. This approach contrasts with their more direct involvement in prescribing decisions within the hospital environment.

Three key objectives were:

1) to enhance PCPs' understanding of prudent antibiotic use at local level by presenting data on antibiotic consumption and AMR in KKC, supplemented by research highlighting negative consequences of imprudent antibiotic use [4];
2) to aid PCPs in understanding national and international guidelines for management of ARIs and AB [42, 43];
3) to provide practical examples aimed at fostering collaborative decision-making among PCPs, patients, and their families regarding antibiotic prescribing.

Throughout the intervention, PCPs were encouraged to actively engage by seeking clarifications and requesting additional local antibiotic use data. The same educational materials that had been previously distributed to all KKC PCPs, including those not participating in the intervention, were once again provided during intervention. These included posters for PCPs' practices and patient-friendly brochures emphasizing prudent antibiotic use. Non-participating PCPs in KKC and all PCPs in BBC did not receive AD intervention.

Data collection

Antimicrobial consumption data for both counties for individual PCPs practices were obtained from Croatian Institute of Public Health. This dataset included information from each visit corresponding to International Statistical Classification of Diseases, 10th Revision (ICD-10) codes for diagnoses J01 (acute sinusitis), J02 (acute pharyngitis), J03 (acute tonsillitis), J06 (acute upper respiratory infection) and J20 (acute bronchitis) [44]. Details encompassed visit dates, group classification (participating or non-participating KKC PCPs, or BBC PCPs), unique patient and case identifiers (noting repeated diagnoses in the same patients), and prescribed antibiotics, if any. Our analysis primarily focused on data with Anatomical Therapeutic Chemical group (ATC) group J01 (broad spectrum antimicrobials) linked to aforementioned diagnoses as they are often viral in origin and prone to inappropriate broad-spectrum antibiotic prescribing in primary health care settings, including KKC and BBC [3, 4]. We assumed that all prescriptions were filled at pharmacies and consumed by patients, acknowledging the constraints in verifying actual medication utilization.

The data on CDI cases, along with the total specimens tested for suspected CDI in both primary and hospital settings across the counties, were gathered from the records of microbiology laboratories in both counties with the assistance of microbiology experts working in those laboratories.

All data were securely stored at the General hospital "dr. Tomislav Bardek" Koprivnica, Croatia.

Outcome measures

The primary outcome measure was the change in the quantity of prescribed antimicrobials, expressed as the adjusted defined daily dose (DDD) for oral use per day, across the specified ICD diagnoses during the described periods, regardless of therapy duration. The secondary outcome measure was change in incidence of CDI cases for patients on antimicrobial therapy across 3 periods. A CDI case was defined by diarrhoea or toxic megacolon, with positive laboratory assays for *C.diff.* toxin A and/or B in stool, or detection of toxin-producing *C.diff.* via culture or Polymerase Chain Reaction (PCR) [45].

Statistical analysis

Dose of each prescribed antibiotic was standardized using DDD. For each group and diagnosis, we calculated the total prescribed DDD per day, referred to herefter as the "daily DDD". Daily DDD exhibited both weekly and yearly seasonality. To adjust for this common seasonality of all groups, we employed general log-linear model with daily DDD as dependent variable and decimal day (to capture trend), day of the week, public holiday status, month, and day in the year (to capture year seasonality). We normalized the days of the year (365 or 366) between 0 and 1, multiplied them by 2π, and applied a cosine transformation. Additionally, the model was also adjusted for study groups and number of cases. Estimated trends and seasonality were removed from daily DDD data by shifting model residuals for model estimated value with fixed day of the week to 'Tuesday', month to 'April', public holiday status to 'FALSE', number of cases set to median number of daily cases in BBC control group (equal to 10, 8, 9, 11 and 4 daily cases for J01, J02, J03, J06 and J20, respectively) and group mean. This approach resulted in what we refer to as "adjusted daily DDD".

To assess the impact of AD intervention, we modelled the adjusted daily DDD using a general log-linear model with adjusted daily DDD as dependent variable, and group and intervention period (nested within the group) as independent variables. Dates corresponding to intervention period (from 01st to 30th April 2020) were excluded from the analyses. Two series of *post-hoc* tests were conducted: a comparison of post- versus pre-intervention periods within groups, and an inter-group comparison of changes from post- to pre-intervention. False discovery rate was controlled by adjusting p values to multiple testing by Benjamini–Hochberg method. P-values < 0.05 were considered significant. Data were summarized and analysed for each diagnosis and for all five diagnoses together.

Data gathered on number of positive and negative tests on *C. diff.* in primary and hospital settings across the counties were analysed using general log-linear model with number of cases (positive tests) as a dependent variable, while setting and county factors (crossed), along with intervention year (nested within each interaction of setting and county) were independent variables. Following model fitting, two series of post-hoc tests were conducted analogue to adjusted daily DDD analyses.

Data analyses were conducted using R language and environment for statistical computing [46–48].

Table 1 Demographics, employment status and location of practice

Sex	**Number (%)**
Female	15 (93,75)
Race or Ethnicity	**Number (%)**
White	16 (100)
Age range	**Number (%)**
25–34	2 (12,50)
35–44	3 (18,75)
45–54	2 (12,50)
55–64	7 (43,75)
65–75	2 (12,50)
Employment status	**Number (%)**
Full-time	16 (100)
Location of practice	**Number (%)**
Urban	11 (68,75)
Suburban	3 (18,75)
Rural	2 (12,50)
Years in Practice	**Number (SD)**
Mean	28,75 (11,38)

Results

Out of fifty-seven PCPs, sixteen PCPs agreed to participate in AD intervention during workshops. These participants had a mean 29 years (SD 11.38) of practice experience (Table 1). The non-participants cited time constraints as a primary reason for non-participation, attributing this to staffing challenges and the demands of data collection/reporting.

Antibiotic prescribing pre-intervention

Pre-intervention, the adjusted DDD per day in the participating KKC group was 35.93 for acute sinusitis (95% CI, 33.21–38.87), 30.27 for acute pharyngitis (95% CI, 28.29–32.39), 37.38 for acute tonsillitis (95% CI, 35.12–39.77), 27.62 for acute upper respiratory infection (95% CI, 25.65–29.74), and 12.77 for acute bronchitis (95% CI, 11.45–14.24). These values were significantly higher for all diagnoses compared to the non-participating KKC PCPs control group but significantly lower than the BBC PCPs second control group (Fig. 1, Graph A). Graph A shows the mean adjusted DDD per day pre- and post-intervention for all five diagnoses, indicating a general decline in antibiotic prescribing post-AD intervention.

Impact of academic detailing

The AD intervention led to a significant reduction ($p < 0.05$) in antibiotic prescribing: 30% for acute pharyngitis, 33% for acute tonsillitis, 23% for acute upper respiratory infection, and 36% for acute bronchitis. While acute sinusitis experienced a 14% reduction post-intervention, this change did not reach statistical significance ($p = 0.62$) (Fig. 1, Graph B). Overall, a significant 25% decrease in antibiotic prescribing was observed across all five diagnoses in the AD intervention group (Fig. 2, Graph B).

Trends in antibiotic prescribing

The most substantial reduction (65%) in antibiotic prescribing post-AD intervention was observed in the "other antibiotics" group, which included doxycycline (81.9% of total prescribed DDD among other antibiotics), clindamycin (8.9%), sulfamethoxazole and trimethoprim (4.7%), fluoroquinolones (4.2%), nitrofurantoin (0.2%), and fosfomycin (0.1%) (Fig. 3, Graphs A and B and Appendix 2–4). Penicillins and their combinations also saw significant reductions. However, changes in prescribing rates for macrolides and cephalosporins were not statistically significant (Fig. 3, Graph B).

Clostridioides difficile infections in primary care and in hospital

The data is presented for the entire counties, as we could not obtain data for each group. In primary care in KKC, the incidence of CDI cases decreased from 57 cases/year pre-intervention to 37 cases/year post-intervention (incidence rate ratio, RR = 0.640, $p = 0.006$). In BBC, the incidence remained unchanged (Fig. 4, Graph A). The inter-county difference in these changes was not statistically significant (ratio = 0.749, 95% CI, 0.460–1.220; $p = 0.246$) (Fig. 4, Graph B).

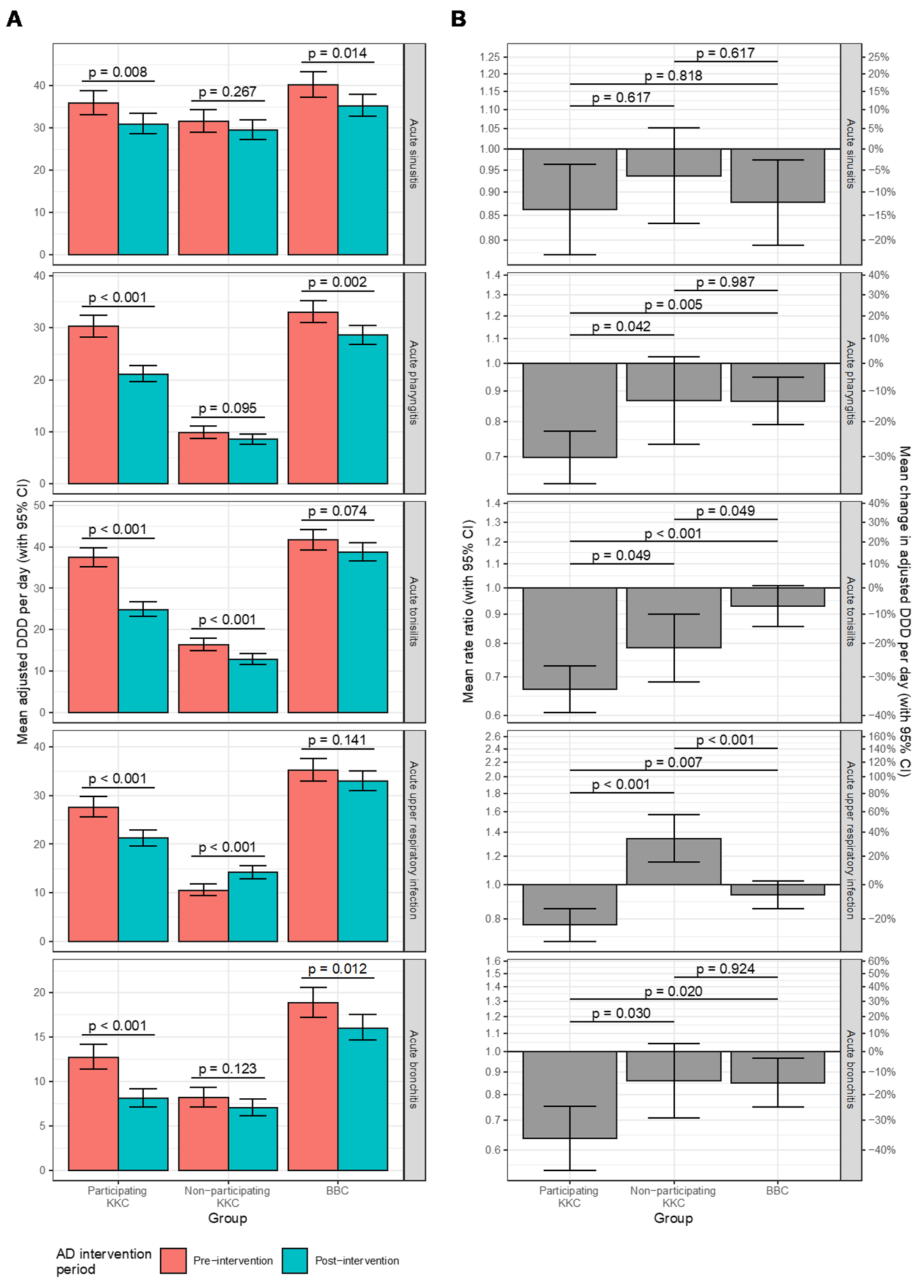

Fig. 1 **A** Part A of the figure illustrates the mean adjusted defined daily dose (DDD) of antibiotics prescribed per day for the diagnosis of acute sinusitis, acute pharyngitis, acute tonsillitis, acute upper respiratory infections, and acute bronchitis. The data is presented before (pre-intervention period from 01st January 2018 to 31st March 2020) and after (post-intervention period from 1st May 2020 to 31st December 2022) the implementation of an academic detailing (AD) intervention across three distinct groups: participating primary care physicians (PCPs) in Koprivnica-Krizevci county (KKC), non-participating PCPs in KKC, and all (non-participating) PCPs in Bjelovar-Bilogora county (BBC). The error bars in the graph represent the 95% confidence interval (CI). Additionally, the statistical significance of the group-wise comparison of mean adjusted DDD/day pre- and post-intervention periods are denoted above the columns of each respective group with the corresponding *p* value. **B** Part B of the figure illustrates the mean post-intervention to pre-intervention adjusted DDD rate ratio, expressed as well as mean change in adjusted DDD rate relative to pre-intervention period (right Y axis) across three distinct groups: participating PCPs in KKC, non-participating PCPs in KKC and PCPs in BBC. Error bars in the graph represent 95% confidence interval. Y-axis is log-transformed. Additionally, the statistical significance of the comparison of mean rate ratios between the groups is denoted above the columns of each group pair with corresponding *p* value. AD – Academic Detailing; DDD—defined daily dose; KKC – Koprivnica-Križevci County; BBC – Bjelovar-Bilogora County; CI—confidence interval

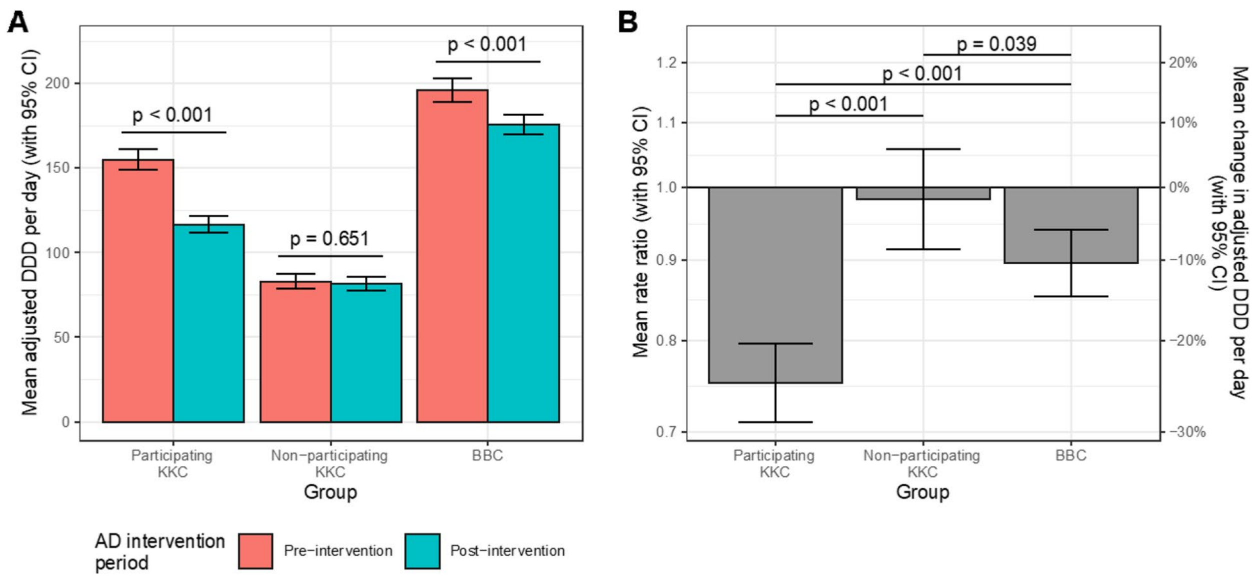

Fig. 2 **A** Part A of the figure illustrates the mean adjusted defined daily dose (DDD) of antibiotics prescribed per day for the all five diagnosis put toogether (acute sinusitis, acute pharyngitis, acute tonsillitis, acute upper respiratory infections, and acute bronchitis). The data is presented before (pre-intervention period from 01st January 2018 to 31st March 2020) and after (post-intervention period from 1st May 2020 to 31st December 2022) the implementation of an academic detailing (AD) intervention across three distinct groups: participating primary care physicians (PCPs) in Koprivnica-Krizevci county (KKC), non-participating PCPs in KKC, and all (non-participating) PCPs in Bjelovar-Bilogora county (BBC). The error bars in the graph represent the 95% confidence interval (CI). Additionally, the statistical significance of the group-wise comparison of mean adjusted DDD/day pre- and post-intervention periods are denoted above the columns of each respective group with the corresponding *p* value. **B** Part B of the figure illustrates the mean post-intervention to pre-intervention adjusted DDD rate ratio, expressed as well as mean change in adjusted DDD rate relative to pre-intervention period (right Y axis) across three distinct groups: participating PCPs in KKC, non-participating PCPs in KKC and PCPs in BBC. Error bars in the graph represent 95% confidence interval. Y-axis is log-transformed. Additionally, the statistical significance of the comparison of mean rate ratios between the groups is denoted above the columns of each group pair with corresponding *p* value. AD – Academic Detailing; DDD—defined daily dose; KKC – Koprivnica-Križevci County; BBC – Bjelovar-Bilogora County; CI—confidence interval

Additionally, we examined the incidence of hospital-acquired CDI, acknowledging its potential emergence from primary care settings exacerbated by antibiotic therapy. In the KKC hospital, there was a decrease in the incidence of CDI cases from 72 cases/year pre-intervention to 63 cases/year post-intervention (RR = 0.881, $p = 0.482$). In contrast, the BBC hospital experienced an increase from 6 cases/year to 20 cases/year during the corresponding period (RR = 3.333, $p = 0.001$) (Fig. 4, Graph A). The observed difference in these changes between the counties was statistically significant (ratio = 0.264, 95% CI, 0.133–0.526; $p < 0.001$) (Fig. 4, graph B).

Discussion

This quasi-experimental feasibility study suggests potential benefits of the implementing hospital educator-led antimicrobial stewardship in a primary care settings. The intervention, which primarily focused on AD, was associated with a reduction in antibiotic prescriptions for ARIs such as acute sinusitis, acute pharyngitis, acute tonsillitis, and acute upper respiratory infection, as well as for AB. The study design aimed to isolate AD's impact by implementing additional marketing interventions five months before AD (November 2019). When calculating, we included these interventions in the pre-intervention period (from 01st January 2018 to 31st March 2020). This temporal separation allowed for an assessment of AD's effects, measured in the post-intervention period (from 1st May 2020 to 31st December 2022). This study design provides initial insights into the potential impact of the AD intervention on antibiotic prescribing patterns. However, additional research would be beneficial to further validate and expand upon these findings.

The AD intervention period during COVID-19 affected our results in various ways. The 25% decrease in antibiotic prescribing is significant considering the healthcare changes during this time. Lockdowns may have reduced respiratory infections, while increased health awareness could have influenced antibiotic demand. Our intervention showed that AD can adapt to changing circumstances and provide guidance to PCPs. These results are relevant to efforts to reduce antibiotic use in southeastern European countries, where consumption and resistance are linked [12, 49, 50]. Our findings showed, a larger decrease in antibiotic prescribing compared to some previous European

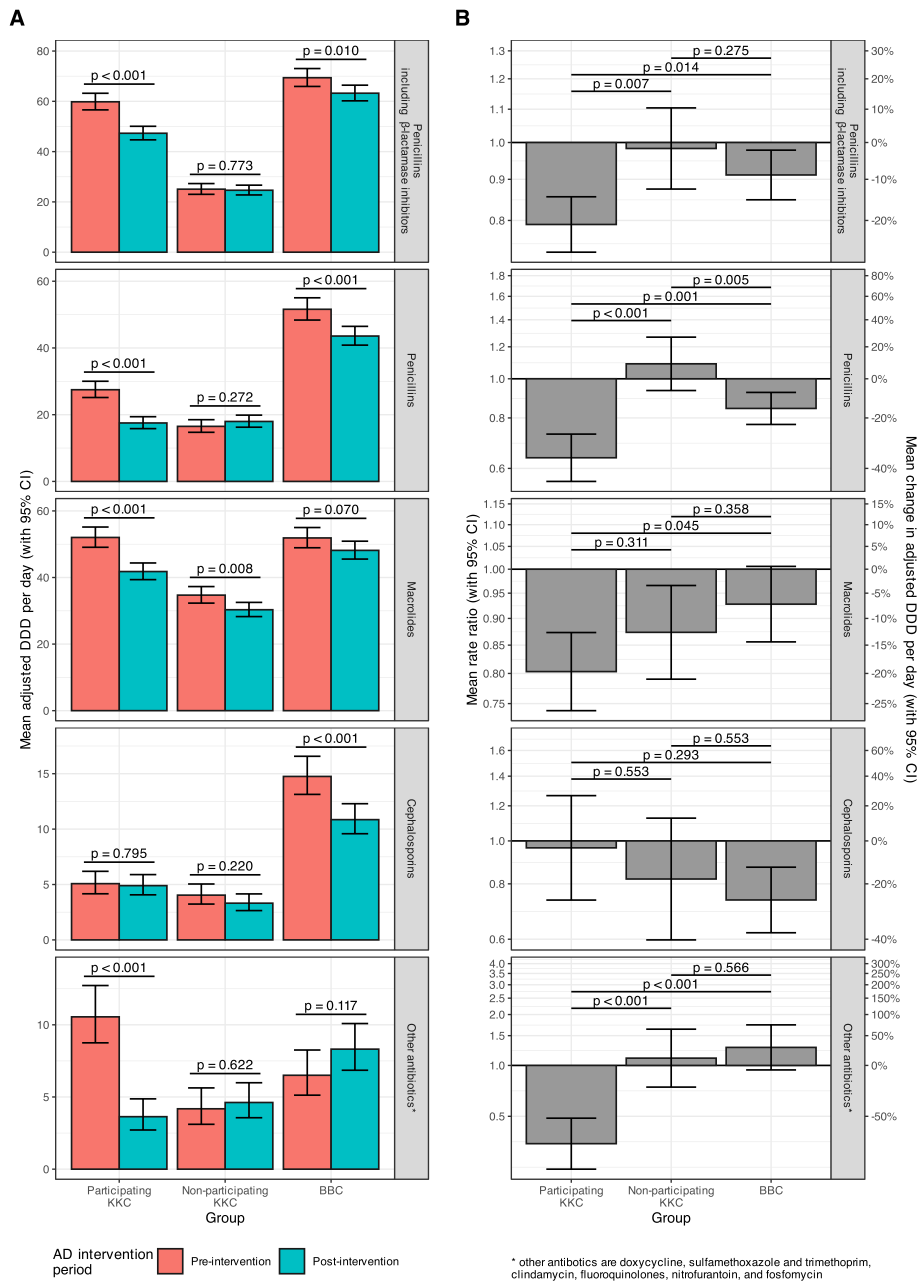

Fig. 3 **A** Part A of the figure illustrates the mean adjusted defined daily dose (DDD) of groups antibiotics (penicillins-including β-lactamase inhibitors, penicillins, macrolides, cephalosporines and other antibiotics) prescribed per day for the all five diagnosis put together (acute sinusitis, acute pharyngitis, acute tonsillitis, acute upper respiratory infections, and acute bronchitis). The data is presented before (pre-intervention period from 01st January 2018 to 31st March 2020) and after (post-intervention period from 1st May 2020 to 31st December 2022) the implementation of an academic detailing (AD) intervention across three distinct groups: participating primary care physicians (PCPs) in Koprivnica-Krizevci county (KKC), non-participating PCPs in KKC, and all (non-participating) PCPs in Bjelovar-Bilogora county (BBC). The error bars in the graph represent the 95% confidence interval (CI). Additionally, the statistical significance of the group-wise comparison of mean adjusted DDD/day pre- and post-intervention periods are denoted above the columns of each respective group with the corresponding *p* value. **B** Part B of the figure illustrates the mean post-intervention to pre-intervention adjusted DDD rate ratio, expressed as well as mean change in adjusted DDD rate relative to pre-intervention period (right Y axis) across three distinct groups: participating PCPs in KKC, non-participating PCPs in KKC and PCPs in BBC. Error bars in the graph represent 95% confidence interval. Y-axis is log-transformed. Additionally, the statistical significance of the comparison of mean rate ratios between the groups is denoted above the columns of each group pair with corresponding *p* value. AD – Academic Detailing; DDD—defined daily dose; KKC – Koprivnica-Križevci County; BBC – Bjelovar-Bilogora County; CI—confidence interval

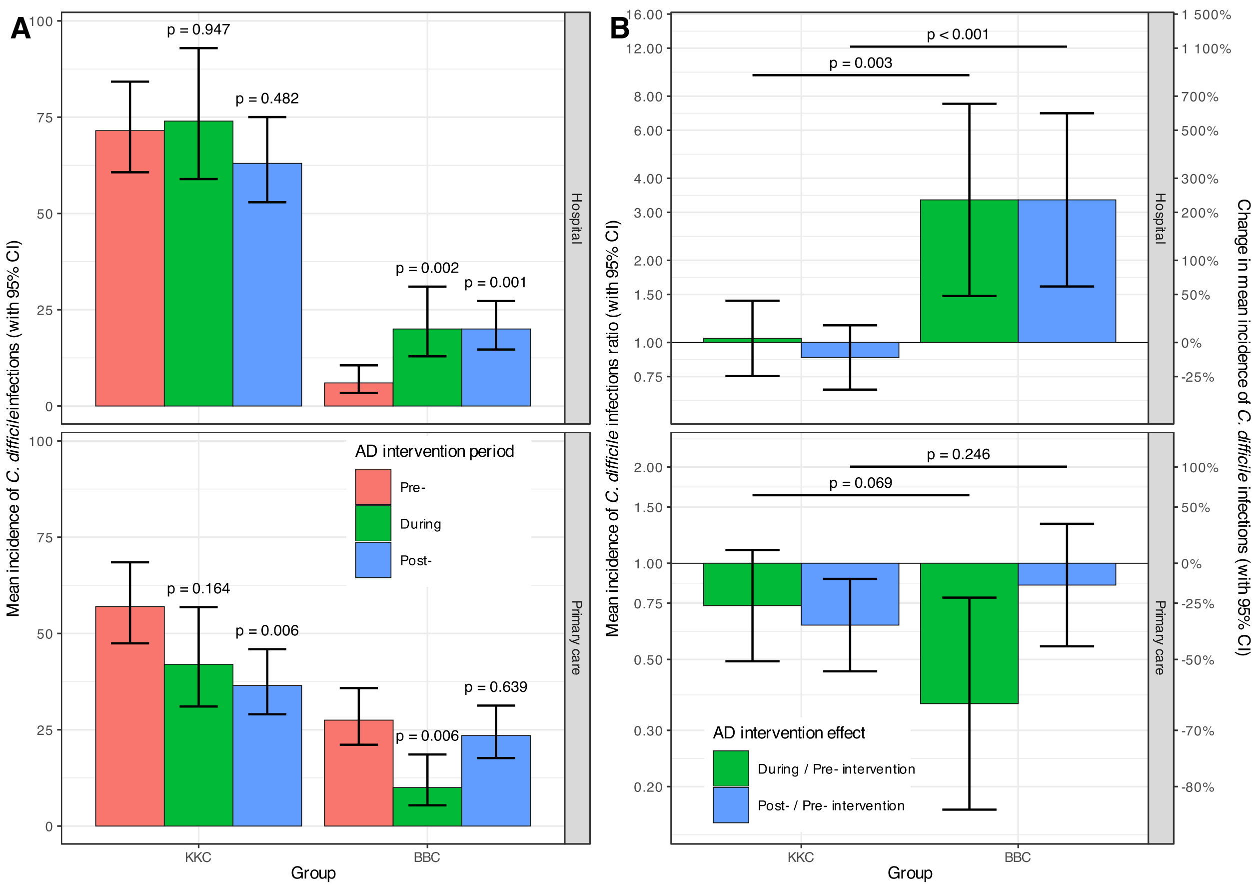

Fig. 4 **A** Part A of the figure illustrates the mean incidence of *Clostridioides difficile* infections *(CDI)* for hospital and primary care. The data is presented before (pre-intervention period from 01st January 2018 to 31st December 2019), during (intervention period from 1st January 2020 to 31st December 2020) and after (post-intervention period from 1st January 2021 to 31st December 2022) the implementation of an academic detailing (AD) intervention across two distinct groups: all (participating and non-participating) primary care physicians (PCPs) in Koprivnica-Krizevci county (KKC) and all (non-participating) PCPs in Bjelovar-Bilogora county (BBC). The error bars in the graph represent the 95% confidence interval (CI). **B** Part B of the figure illustrates the mean post-intervention to pre-intervention mean change in incidence (as well as incidence rate ratio (RR)) across two distinct groups: all PCPs in KKC and all PCPs in BBC. Error bars in the graph represent 95% confidence interval. Y-axis is log-transformed. Additionally, the statistical significance of the comparison of mean odds ratios between the groups is denoted above the columns of each group pair with corresponding *p* value. AD – Academic Detailing; KKC – Koprivnica-Križevci County; BBC – Bjelovar-Bilogora County; CI—confidence interval

trials (1–2% reduction) and align with certain US studies (10–41% reduction) [28–31]. However, it is important to note that our study had a broader scope than US studies, which focused on fewer antibiotics or had different control group structure [31]. Moreover, during the early stages of pandemic, when our study was conducted, access to rapid COVID-19 testing was limited. This led to challenges for healthcare providers due to the overlap in symptoms between SARS-CoV-2 infections and ARIs. Typically, such uncertainty might lead to an increase in empirical antibiotic prescriptions for suspected bacterial infections, as clinicians prefer to be cautious. However, our results indicate a different trend, suggesting that the AD intervention was effective despite these pressures. Although the pandemic setting may affect the generalizability of our findings, it provided a unique opportunity to test the resilience of our AD approach in promoting judicious antibiotic use under extraordinary circumstances. This context enhances our results, suggesting that AD can be an effective tool in ASP even during healthcare crises. The most notable decline in antibiotic prescribing for ARIs and AB was observed in the "other antibiotics" category, which includes doxycycline, clindamycin, sulfamethoxazole and trimethoprim, fluoroquinolones, nitrofurantoin and fosfomycin. Although this category had a lower overall number of antimicrobial consumption compared to combinations of penicillins (including beta-lactamase inhibitors) and macrolides, their appropriate use is crucial for prudent antibiotic practice. For example, nitrofurantoin and fosfomycin, antibiotics typically used for uncomplicated lower urinary tract infection in women, were sometimes inappropriately prescribed for ARIs and AB [51]. This may have been due to insufficient knowledge among PCPs about current guidelines for respiratory infections or misunderstanding about the appropriate indications for these drugs. Furthermore, there may have been a misconception regarding the effectiveness of nitrofurantoin and fosfomycin against respiratory pathogens.

Additionally, during the AD intervention, the A-team emphasized the negative effects of inappropriate antibiotic use, particularly adverse effects, drug interactions and high risk of AMR associated with fluoroquinolones. This educational approach likely contributed to the significant decline in prescribing for "other antibiotics" for ARIs post-intervention.

This study is the first local, hospital educator-led AD program that resulted in decreased number of antibiotics prescribed in primary care. Interestingly, our results suggest that, prior to AD intervention, participating KKC PCPs exhibited higher antibiotic prescribing pattern compared to non-participating KKC PCPs but lower pattern compared to BBC PCPs for all specified diagnoses. This suggest that participating PCPs might have become more aware of their overprescribing practices and were open to improvement. However, this observation should be interpreted cautiously due to potential recruitment bias. The PCPs who volunteered for the study were more inclined towards changing their prescribing habits, which could act as a confounding variable. This can overstate impact of AD intervention. Nevertheless, the post-intervention reduction within the KKC group highlights the potential of targeted educational interventions to positively influence local prescribing behaviours.

This feasibility study underscores the importance of adapting implementation strategies to local contexts, recognizing that standardized approaches may not always be effective. It emphasize the need to tailor implementation methods to the specific requirements and conditions of each healthcare system. This approach may benefit patients and contribute to the overall healthcare improvement. Moreover, previous efforts to raise awareness among prescribing doctors have had limited impact on their prescription behaviour [52]. Our study explored individual approach, which proved effective. Consistent with both this study and previous research, evidence-based behaviour change techniques that emphasize health consequences were successful in improving prescribing practices, especially when directed at individual physicians rather than larger groups or institutions [31, 52, 53].

Although, this study can not determine the impact of the AD intervention on CDI rates, we sought to discover whether the intervention's effect trended towards reduction, specifically examining if there was a greater decrease in CDI rates in KKC compared to BBC. Our findings suggest that addressing CDI requires a multifaceted approach. Furthermore, considering the potential for CDI transmission between primary care and hospital environments, our results indicate that CDI incidence in hospitals may not solely reflect the effectiveness success or failure of primary care intervention. This aligns with results of another study, which suggested that up to half of community CDI cases may go undetected due to lack of clinical suspicion accounting for approximately three times more undiagnosed adults in the community than in hospitals [54]. Further research is needed to identify specific factors influencing CDI trends in both primary care and hospital settings. Such insights could inform the development of more targeted and effective interventions across healthcare sectors.

Education, though not a standalone solution for antibiotic misuse, is an an important part of a multifaceted approach to address this issue. It provides healthcare workers with the knowledge necessary to make informed decisions about antibiotic prescribing. Our study, which is among the first of its kind in this region, indicates that educational strategies focusing on AD interventions are both feasible and potentially effective [55]. These interventions may contribute to reducing unnecessary antibiotic prescriptions. Furthermore, PCPs who are well-educated in current antibiotic prescribing guidelines can become valuable advocates for ASP within their healthcare facilities. They can actively contribute to the development and implementation of ASP and infection prevention strategies. Their expertise in managing common infections in community settings can provide valuable insights for creating effective policies and protocols.When integrated with other interventions such as improved diagnostics, surveillance, and policy measures, education becomes important element in addressing AMR. However, it's important to note that the effectiveness of these interventions may vary depending on local contexts and healthcare systems. Continuous evaluation and adaptation of these strategies are necessary to ensure their ongoing relevance and efficacy in the improving antibiotic prescribing.

Limitations and advantages

Several factors may have influenced the study results, including the study design, characteristics of the study population, and the intervention implementation. We acknowledge that the non-randomized nature of the study, may have introduced a some selection bias as participants who chose to engage in the intervention might have had a heightened interest in antibiotic stewardship. While our focus on a single county with a small population, allowed for a detailed analysis, it may limit the broader applicability of our findings.

The unique healthcare infrastructure, prescribing habits, and patient demographics in this area might affect the applicability of the results to other regions or healthcare settings. We adapted our data presentation to DDD/day due to limitations in patient coverage information, but ensured comparability by adjusting our analysis to a control group of known population size.

The study's results may also have been influenced by other variables not accounted for, such as parallel healthcare initiatives, policy changes, or seasonal variations in infection rates, which could have impacted antibiotic prescribing practices and CDI rates. However, our study's design, particularly the use of two control groups helped mitigate the impact of these confounding variables.

One of our study's strengths lies in its use of local hospital educators to implement the intervention. This approach likely enhanced the credibility and relevance of the program, as these educators understand the local healthcare context and challenges.

Furthermore, our findings align with larger US studies, suggesting that out intervention approach has a potential for broader application, particularly in similar southeastern European healthcare settings [31, 32]. While we have identified areas for improvement and further investigation, our study provides valuable insights into the potential of targeted educational interventions in improving ASP.

Conclusion

This feasibility study explores the potential effectiveness of AD intervention in primary healthcare for addressing antibiotic overprescribing. Despite the challenges caused by the COVID-19 pandemic, the findings suggests that targeted, educator-led AD programs may help reduce antibiotic misuse, especially for viral respiratory conditions.

Our study highlights the importance of adapting healthcare strategies to local contexts to improve antimicrobial stewardship, with a focus on Croatia and southeastern Europe. This approach may contribute to more sustainable healthcare practices and aid in addressing the challenge of AMR.

While AD is not a new concept, our study combines hospital-based leadership, regional adaptation and consideration of COVID-19 impacts. It also examines the potential for broad impact in southeastern Europe, where such interventions have been less studied. Additional research with larger sample sizes and in diverse settings in this region would be valuable to validate these findings and explore their wider applicability.

This study contributes to the ongoing efforts to promote judicious antibiotic use and improve antimicrobial stewardship in primary care settings, which may help address the global challenge of AMR.

Abbreviations

A-team	Antimicrobial stewardship team
AB	Acute bronchitis
AD	Academic detailing
AMR	Antimicrobial resistance
ASP	Antimicrobial stewardship program
ARI	Acute upper respiratory infection
ATC	Anatomical Therapeutic Chemical group
BBC	Bjelovar-Bilogora County
C.diff.	*Clostridioides difficile*
CDI	*Clostridioides difficile* Infection
CI	Confidence interval
COVID-19	Coronavirus disease 2019
DDD	Defined daily dose
EEA	European Economic Area
EU	European Union Member States
ICD-10	International Statistical Classification of Diseases, 10th Revision codes
KKC	Koprivnica-Križevci County
PCP	Primary care physician
PCR	Polymerase Chain Reaction
WHO	World Health Organisation

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Authors' contributions

A study design was developed by DKP, MK, APA, VM, VJP. Data collection was done by DKP, KG and ŽD. Data analysis and writing were done by DKP and DK. Reviewing an editing was done by MK, MPP, ATA, JMP, VBV and SM. All authors read and approved the final manuscript.

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Data availability

Data are securely stored at the General hospital "dr. Tomislav Bardek" Koprivnica, Croatia. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The research underwent review and approval by the Regional Committee for Medical and Health Research Ethics for Outpatient Clinics of Koprivnica-Križevci County (reference number 2137–16-5266/2021). All participants provided informed consent. Additionally, we obtained ethical approval for data collection from Croatian Institute of Public Health (reference numbers 030–02/23–15/8 and 117–15-23–2), and informed consent was secured from all identified PCPs in KKC and BBC. No personal data of PCPs or patients were included. We identified prescriptions for patients diagnosed with ARI and AB linking them to PCPs using unique identifiers. Furthermore, adhering to

STROBE-AMS guidelines, the study aimed to enhance reporting on the link between antimicrobial resistance and antibiotic use, contributing to ASP improvements [40, 41].

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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