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Factors associated with antibiotic prescribing in patients with acute respiratory tract complaints in Malta: a 1-year repeated cross-sectional surveillance study

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ABSTRACT

Objective To identify factors that influence general practitioners' (GPs') oral antibiotic prescribing for acute respiratory tract complaints (aRTCs) in Malta.

Design Repeated, cross-sectional surveillance.

Setting Maltese general practice; both public health centres and private GP clinics.

Participants 30 GPs registered on the Malta Medical Council's Specialist Register and 3 GP trainees registered data of 4831 patients of all ages suffering from any aRTC. Data were collected monthly between May 2015 and April 2016 during predetermined 1-week periods.

Outcome measures The outcome of interest was antibiotic prescription (yes/no), defined as an oral antibiotic prescription issued for an aRTC during an in-person consultation, irrespective of the number of antibiotics given. The association between GP, practice and consultation-level factors, patient sociodemographic factors and patient health status factors, and antibiotic prescription was investigated.

Results The antibiotic prescription rate was 45.0%. Independent factors positively associated with antibiotic prescribing included female GP sex (OR 2.3, 95% CI 1.22 to 4.26), GP age with GPs ≥60 being the most likely (OR 34.7, 95% CI 14.14 to 84.98), patient age with patients ≥65 being the most likely (OR 2.3, 95% CI 1.71 to 3.18), number of signs and/or symptoms with patients having ≥4 being the most likely (OR 9.6, 95% CI 5.78 to 15.99), fever (OR 2.6, 95% CI 2.08 to 3.26), productive cough (OR 1.3, 95% CI 1.03 to 1.61), otalgia (OR 1.3, 95% CI 1.01 to 1.76), tender cervical nodes (OR 2.2, 95% CI 1.57 to 3.05), regular clients (OR 1.3, 95% CI 1.05 to 1.66), antibiotic requests (OR 4.8, 95% CI 2.52 to 8.99) and smoking (OR 1.4, 95% CI 1.13 to 1.71). Conversely, patients with non-productive cough (OR 0.3, 95% CI 0.26 to 0.41), sore throat (OR 0.6, 95% CI 0.53 to 0.78), rhinorrhoea (OR 0.3, 95% CI 0.23 to 0.36) or dyspnoea (OR 0.6, 95% CI 0.41 to 0.83) were less likely to receive an antibiotic prescription.

Conclusion Antibiotic prescribing for aRTCs was high and influenced by a number of factors. Potentially inappropriate prescribing in primary care can be addressed through multifaceted interventions addressing modifiable factors associated with prescription.

Strengths and limitations of this study

- ► This is the first study in Malta that looks at factors influencing antibiotic prescribing using repeated cross-sectional surveillance data.
- ► The simple to complete surveillance forms were intended to aid documentation of as many acute respiratory tract complaint cases as possible, while reducing general practitioner (GP) drop-outs and non-reporting. Given its design and incorporation into clinical practice, it may have helped to reduce the effect of observation bias.
- ► GP participation was voluntarily; therefore, it is possible that the GP sample consists of GPs who were more interested in the research area or more conservative prescribers than non-participating GPs, affecting the study's representativeness.
- ► The audit-based nature of the study may have resulted in measurement error; GPs may have completed patient background information themselves without directly asking the patient and variables located at the end of the surveillance sheet that were left unmarked may have been inaccurately assumed to be non-cases.
- ► Since GPs were issued 3 monthly feedback reports, a behavioural change intervention itself, their antibiotic prescribing rate may have been affected as a result.

Trial registration number NCT03218930

INTRODUCTION

Since their discovery, antibiotics have saved lives and reduced suffering; however, their considerable overuse and misuse has, in part, led to the development of antibiotic resistance, threatening their effectiveness globally. Unchecked, antibiotic resistance can halt and potentially reverse decades of medical progress, with severe repercussions on patient outcomes and healthcare expenditure both on an individual and societal level.[1] Antibiotics do not only target pathogenic bacteria; their use has long-lasting effects on gut flora and has been shown to be associated with allergy development and metabolic syndromes for example, particularly when prescribed during infancy.[2]

In Europe, a positive correlation between antibiotic use and resistance has been shown.[3] Most antibiotic prescriptions are provided in outpatient care, with respiratory tract infections being the most common diagnoses.[3] Studies have shown that up to 78% of patients are prescribed antibiotics for respiratory tract infections in primary care, even though an estimated 90% are viral in aetiology and thus antibiotics are seldom required.[4–8] Indeed, unless pneumonia is suspected, the effect of antibiotic treatment is moderate at best indicating that many antibiotic prescriptions are provided unnecessarily and without any overall patient benefit.[9] Consequently, a key strategy to contain antibiotic resistance is to improve antibiotic use in primary care, particularly among general practitioners (GPs).

While primary care guidelines often recommend limited antibiotic use in the treatment of respiratory tract infections, substantial variation exists in practical case management across countries and the evidence of overprescribing is abundant.[7 10 11] The decision to prescribe an antibiotic is complex and influenced by a host of interconnected factors including, but not limited to, provider attitudes and characteristics, patient age, comorbidities, signs and symptoms, expectations, environmental and cultural factors.[10 12–15] Further cloaked by diagnostic uncertainty, GPs risk misdiagnosing and misclassifying the aetiology of respiratory tract infections, and may prescribe antibiotics to be on the safe side.

In the latest Special Eurobarometer survey on antibiotic resistance held in 2018, Malta reported the second highest antibiotic consumption in Europe with 42% of Maltese respondents reporting taking at least one antibiotic course in a calendar year.[16] Non-prescribed use was minimal at 4%.[16] Our recently published descriptive study based on surveillance data showed that, in 2015/2016, 46% of patients with acute respiratory tract complaints (aRTCs) were prescribed antibiotics by their GP.[5] The top three diagnoses that received an antibiotic prescription were tonsillitis (96%), otitis media (93%) and bronchitis (88%), and the most commonly prescribed antibiotics were macrolides (36%) and penicillins with a β-lactamase inhibitor (33%).[5] Indeed, the majority of antibiotic consumption in Malta occurs in the community and comprises primarily broad-spectrum antibiotics (ie, tetracyclines, beta-lactam antibacterials, second-generation and third-generation cephalosporins, macrolides and fluoroquinolones).[5 17 18]

Nationwide data on antibiotic prescribing in Maltese primary care are lacking and Malta has only been able to provide the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) with wholesale distributor data to estimate community antibiotic use. As a result, it has not been possible to run in-depth analysis to elucidate factors that impact antibiotic prescribing. Recognising the need to identify and understand the drivers of antibiotic prescribing in primary care to develop targeted antibiotic stewardship activities and improve their chance of success, we decided to carry a more in-depth analysis of our 2015/2016 surveillance data. Therefore, this study aimed to identify factors that influence GPs' oral antibiotic prescribing for aRTCs in Malta.

METHODS

Study design, setting and participants

This cross-sectional surveillance study provided baseline data for the Maltese Antibiotic Stewardship Programme in the Community (MASPIC) project, a quasi-experimental social marketing intervention aiming to reduce inappropriate antibiotic prescribing in Maltese primary care. A study protocol with a detailed description of the study setting and design has already been published.[19] An in-depth description of GPs' antibiotic prescribing patterns at baseline, using the same surveillance data but with slightly different eligibility criteria, has been presented elsewhere.[5]

In brief, this study was carried out in public and private general practices in Malta. A total of 370 GPs registered on the Malta Medical Council's Specialist Register and 34 GP trainees were invited to the study. Seventy registered GPs and GP trainees responded, of which 35 agreed to participate. Prior to surveillance initiation, 2 GPs stopped working clinically; therefore, ultimately 30 GPs and 3 GP trainees participated.

Patient and public involvement

This study was conducted without patient or public involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret results. Patients were neither requested to contribute to the writing or editing of this document for readability or accuracy.

Data collection

During enrolment, GPs were asked to complete a background information sheet, which included information on demographics, training/experience and service delivery organisation (online supplementary figure S1). GPs registered patients seen for aRTCs during 12 predetermined surveillance weeks (1 week/month without substitutions) between May 2015 and April 2016. Forms were completed by the GPs themselves during the first consultation with patients of all ages suffering from any aRTC (defined as lower and upper respiratory tract infections, allergies and exacerbation of chronic obstructive pulmonary disease (COPD)/asthma/bronchitis), and included information on patient and clinical factors, clinical assessment, diagnosis and prescribed medicines. The surveillance data collection form has been published elsewhere.[5] Data on the total number of patients seen each day, regardless of complaint, were also collected.

Communication was maintained with GPs throughout surveillance. Each surveillance week, GPs received 3 text messages, one to remind them to prepare for data collection, another to initiate it and a third to conclude it. GPs were also contacted by phone at most 4 times during the year, to provide encouragement and address queries. Moreover, GPs received 3 monthly individual-level and aggregate-level feedback reports on their prescribing patterns.

Eligibility criteria

Only cases diagnosed with an aRTC were included in this study. Cases were only considered for analysis if they were consulting with the participating GP for the first time for that presenting complaint. Any follow-up visits recorded were automatically excluded. For the purpose of this analysis, all cases diagnosed with pneumonia were excluded from the dataset. Cases where more than one aetiology and/or diagnosis was provided or who were consulted over the phone, were also excluded from analysis. As a result, 313 aRTC cases were excluded from analysis following data cleaning, reducing our final sample size to 4518.

Statistical analysis

Data were analysed using Microsoft Excel 2010 and Stata/IC V.13.1. Surveillance items not marked were assumed not present and analysed as absent. Analyses were conducted using complete-case analysis. Descriptive statistics were calculated using frequencies and percentages, means and SDs, medians and IQRs as appropriate. The outcome of interest was antibiotic prescription (yes/no), defined as an oral antibiotic prescription issued for an aRTC during an in-person consultation, irrespective of the number of antibiotics given. It included both regular and delayed antibiotic prescriptions, the latter to be dispensed if symptoms persisted, typically after 48–72 hours. It did not include ‘delayed instruction’, that is, directions to follow-up for a prescription if symptoms persisted or worsened.

To control for clustering at the GP level, potential predictors of antibiotic prescription were assessed using population averaged models using generalised estimating equations. Frequency distributions of individual explanatory variables of interest were calculated and univariable associations between each variable and antibiotic prescription were subsequently assessed using unadjusted ORs and 95% CIs. Since we could not assume linearity to the outcome, all continuous variables were categorised. Individual signs and symptoms variables were only investigated if at least 5% of aRTC cases presented with that particular symptom. Multivariate Wald-type tests were performed on multilevel categorical variables to test the hypothesis of the overall association.

Potential predictors were included in the multivariable model if significant at $p<0.2$ at univariable level and excluded if there were issues with collinearity. A predictor was only kept in the multivariable model if it improved the model and its p value was less than 0.05. Ultimately, 4425 aRTC cases were included in the final multivariable model.

RESULTS

In this cohort of aRTC patients, 2034 (45.0%) received an antibiotic prescription, of which 333 (16.4%) were delayed.

GP characteristics

Most GPs were male (n=24; 73%). Mean age (years) was 49±12 and mean years of GP practice was 23±11. Eleven (33%) GPs worked exclusively in the public sector while 20 (61%) worked in the private sector (including private pharmacy clinics). Two (6%) worked in both sectors. Online supplementary table S1 summarises the GP characteristics.

Patient characteristics

Just over half of patients were female (n=2395; 53.1%) and the median age was 29 years (IQR=12–48). Over a third had completed up to secondary school education (n=3050; 68.0%). Smoking was reported in 735 (16.5%) cases. A summary of the patients’ sociodemographic and lifestyle characteristics is presented in online supplementary file 1.

Factors associated with antibiotic prescribing

The univariable and multivariable associations between GP, practice and consultation-level factors (table 1), patient sociodemographic factors (table 2), clinical factors (table 3) and antibiotic prescription are described below.

Univariable analysis revealed numerous factors associated with antibiotic prescribing. At GP level, GP age was identified as an important predictor with GPs aged 60 and older being most likely to prescribe antibiotics. At consultation level, regular clients and patients who asked for antibiotics were more likely to receive an antibiotic prescription. Patient sociodemographic factors associated with antibiotic prescription included female sex, patient age (particularly those aged 65 and older) and being a smoker. Finally, a number of patient health status factors were significantly associated with antibiotic prescription at univariable level, with the most important being fever >38.5°C, tender cervical nodes and total number of signs and/or symptoms with the odds of prescription increasing as the number increased.

In the final multivariable model, female GPs were 2.3 times more likely to prescribe antibiotics (95% CI 1.22 to 4.26) and, compared with younger GPs aged between 28 and 39 years, GPs aged 5–59 (OR 2.1, 95% CI 1.19 to 3.77) or 60 years and older (OR 34.7, 95% CI 14.14 to 84.98) were more likely to prescribe antibiotics. Increasing patient age also increased the likelihood of receiving an antibiotic prescription, with patients aged 65 and older being the most likely to receive a prescription (OR 2.3, 95% CI 1.71 to 3.18). The more signs and/or symptoms a patient presented with, the more likely they were to be given an antibiotic, with patients having four or more signs and/or symptoms being the most likely (OR 9.6, 95% CI 5.78 to 15.99). Additionally, patients with fever

Table 1 Univariable and multivariable analyses of GP, practice and consultation-level factors associated with antibiotic prescription

	AB prescribed	AB not prescribed	Univariable analysis*		Multivariable analysis†	
	n (%)	n (%)	OR (95% CI)	P value	OR (95% CI)	P value
GP sex						
Male	1666 (45.1)	2028 (54.9)	1	0.762	1	**0.010**
Female	368 (44.7)	456 (55.3)	1.10 (0.58 to 2.10)		2.28 (1.22 to 4.26)	
GP age (years)						
28–39	188 (23.9)	600 (76.1)	1	0.000‡	1	**0.000‡**
40–49	494 (42.2)	678 (57.8)	1.97 (1.05 to 3.70)		1.45 (0.71 to 2.96)	
50–59	1018 (47.5)	1125 (52.5)	2.53 (1.42 to 4.51)		2.12 (1.19 to 3.77)	
≥60	334 (80.5)	81 (19.5)	9.57 (3.78 to 24.21)		34.67 (14.14 to 84.98)	
Years of practice as a GP (n=4502)						
<10	183 (23.7)	589 (76.3)	1	0.026‡	–	–
10–19	301 (40.3)	446 (59.7)	1.77 (0.73 to 4.32)			
20–29	1051 (49.5)	1074 (50.5)	2.81 (1.34 to 5.92)			
≥30	494 (57.6)	364 (42.4)	3.05 (1.32 to 7.05)			
Total no of patients examined per day (n=4436)						
<22	1090 (49.0)	1135 (51.0)	1	0.488	–	–
≥22	913 (41.3)	1298 (58.7)	0.95 (0.83 to 1.09)			
Type of employment						
Full time	1437 (42.2)	1966 (57.8)	1	0.217	–	–
Part time	597 (53.5)	518 (46.5)	1.45 (0.80 to 2.60)			
Type of practice§						
Group	643 (39.5)	987 (60.5)	1	0.062	–	–
Solo	1391 (48.2)	1497 (51.8)	1.73 (0.97 to 3.08)			
Location of GP practice						
Public health centre clinic	318 (34.2)	611 (65.8)	1	0.063‡	–	–
Private GP clinic	897 (46.1)	1050 (53.9)	1.98 (0.97 to 4.01)			
Private pharmacy clinic	819 (49.9)	823 (50.1)	2.27 (1.10 to 4.68)			
Location of consultation (n=4263)						
Clinic	1428 (44.8)	1759 (55.2)	1	0.016	–	–
Home	466 (43.3)	610 (56.7)	1.20 (1.03 to 1.38)			
Regular client						
No	991 (38.9)	1558 (61.1)	1	0.021	1	**0.016**
Yes	1043 (53.0)	926 (47.0)	1.23 (1.03 to 1.48)		1.32 (1.05 to 1.66)	
Antibiotics requested						
No	1983 (44.6)	2459 (55.4)	1	0.000	1	**0.000**
Yes	51 (67.1)	25 (32.9)	2.46 (1.57 to 3.86)		4.76 (2.52 to 8.99)	

*n=4518 unless otherwise specified.
†n=4425 in final multivariable population-averaged panel-data model using generalised estimating equations which was also adjusted for patient age, smoking status, no of signs and symptoms, fever (>38.5°C), productive cough, non-productive cough, sore throat, rhinorrhoea, otalgia, tender cervical nodes and dyspnoea.
‡Wald test; p values highlighted bold indicate independent variables statistically significant at p<0.05; '–' predictor excluded from model.
§GPs working in public sector health centres were defined as group practice practitioners.
AB, antibiotic; GP, general practitioner.

Table 2 Univariable and multivariable analyses of patient sociodemographic factors associated with antibiotic prescription

	AB prescribed	AB not prescribed	Univariable analysis*		Multivariable analysis†	
	n (%)	n (%)	OR (95% CI)	P value	OR (95% CI)	P value
Sex (n=4508)						
Male	910 (43.1)	1203 (56.9)	1	0.037	–	–
Female	1118 (46.7)	1277 (53.3)	1.12 (1.01 to 1.25)			
Age (years) (n=4511)						
<5	194 (35.7)	350 (64.3)	1	0.000‡	1	**0.000‡**
5–11	247 (43.3)	324 (56.7)	1.37 (1.09 to 1.72)		1.55 (1.15 to 2.08)	
12–17	164 (45.9)	193 (54.1)	1.40 (1.08 to 1.80)		1.74 (1.24 to 2.44)	
18–24	215 (46.0)	252 (54.0)	1.47 (1.16 to 1.87)		1.71 (1.24 to 2.36)	
25–44	586 (45.6)	699 (54.4)	1.61 (1.33 to 1.96)		1.82 (1.40 to 2.37)	
45–64	367 (46.5)	423 (53.5)	1.56 (1.26 to 1.92)		1.72 (1.30 to 2.29)	
≥65	260 (52.3)	237 (47.7)	1.86 (1.47 to 2.35)		2.33 (1.71 to 3.18)	
Educational level (n=4484)						
Preschool	181 (36.5)	315 (63.5)	1	0.002‡	–	–
Primary	327 (43.5)	424 (56.5)	1.23 (0.99 to 1.53)			
Secondary	850 (47.1)	953 (52.9)	1.43 (1.18 to 1.74)			
Upper secondary	351 (45.2)	425 (54.8)	1.38 (1.11 to 1.71)			
Tertiary	268 (49.2)	277 (50.8)	1.57 (1.24 to 1.98)			
None achieved	46 (40.7)	67 (59.3)	1.20 (0.81 to 1.79)			
No of persons per household (n=4465)						
1–2	551 (50.7)	536 (49.3)	1	0.000‡	–	–
3–4	1131 (42.1)	1556 (57.9)	0.74 (0.65 to 0.85)			
≥5	328 (47.5)	363 (52.5)	0.91 (0.76 to 1.09)			
Contact with children <5 years (n=4481)						
No	1290 (44.8)	1591 (55.2)	1	0.198	–	–
Yes	727 (45.4)	873 (54.6)	0.93 (0.82 to 1.04)			
Current smoker (n=4453)						
No	1614 (43.4)	2104 (56.6)	1	0.000	1	**0.002**
Yes	402 (54.7)	333 (45.3)	1.64 (1.42 to 1.91)		1.39 (1.13 to 1.71)	

*n=4518 unless otherwise specified.
†n=4425 in final multivariable population-averaged panel-data model using generalised estimating equations which was also adjusted for GP sex, GP age, regular client, antibiotics requested, no of signs and symptoms, fever (>38.5°C), productive cough, non-productive cough, sore throat, rhinorrhoea, otalgia, tender cervical nodes and dyspnoea.
‡Wald test; p values highlighted bold indicate independent variables statistically significant at p<0.05; '–' predictor excluded from model.
AB, antibiotic; GP, general practitioner.

>38.5°C (OR 2.6, 95% CI 2.08 to 3.26), productive cough (OR 1.3, 95% CI 1.03 to 1.61), otalgia (OR 1.3, 95% CI 1.01 to 1.76), tender cervical nodes (OR 2.2, 95% CI 1.57 to 3.05), regular clients (OR 1.3, 95% CI 1.05 to 1.66), patients who requested antibiotics (OR 4.8, 95% CI 2.52 to 8.99) and smokers (OR 1.4, 95% CI 1.13 to 1.71), were also more likely to be prescribed an antibiotic. Conversely, patients with non-productive cough (OR 0.3, 95% CI 0.26 to 0.41), sore throat (OR 0.6, 95% CI 0.53 to 0.78), rhinorrhoea (OR 0.3, 95% CI 0.23 to 0.36) or dyspnoea (OR 0.6, 95% CI 0.41 to 0.83) were less likely to be given an antibiotic prescription.

DISCUSSION

This is the first study in Malta that identifies factors associated with antibiotic prescribing for aRTCs in the community, using surveillance data. While univariable analysis revealed numerous factors associated with antibiotic treatment, multivariable analysis identified several independent predictors of antibiotic prescription at different levels—provider, patient, consultation and clinical.

Our results pertaining to GP factors both converge and diverge from prior research. It has been suggested that high consultation rates may result in higher antibiotic prescription and in fact a Norwegian study was able to

Table 3 Univariable and multivariable analyses of clinical factors associated with antibiotic prescription

	AB prescribed	AB not prescribed	Univariable analysis*		Multivariable analysis†	
	n (%)	n (%)	OR (95% CI)	P value	OR (95% CI)	P value
Comorbidities (n=4218)						
No	1473 (44.5)	1834 (55.5)	1	0.004	–	–
Yes	442 (48.5)	469 (51.5)	1.23 (1.07 to 1.41)			
Duration of symptoms (days) (n=4470)						
<1	135 (35.3)	248 (64.7)	1	0.160‡	–	–
1–3	1369 (46.4)	1581 (53.6)	1.26 (1.02 to 1.55)			
4–7	362 (45.0)	443 (55.0)	1.25 (0.98 to 1.59)			
≥8	144 (43.4)	188 (56.6)	1.34 (1.01 to 1.78)			
No of signs and symptoms (n=4497)						
1	405 (37.1)	687 (62.9)	1	0.000‡	1	**0.000**
2	700 (39.8)	1060 (60.2)	2.25 (1.90 to 2.68)		2.89 (2.26 to 3.69)	
3	591 (51.1)	565 (48.9)	4.15 (3.42 to 5.03)		6.72 (4.73 to 9.55)	
≥4	331 (67.7)	158 (32.3)	6.32 (4.97 to 8.02)		9.62 (5.78 to 15.99)	
Fever (>38.5°C)						
No	1070 (33.4)	2138 (66.6)	1	0.000	1	**0.000**
Yes	964 (73.6)	346 (26.4)	4.74 (4.12 to 5.45)		2.60 (2.08 to 3.26)	
Productive cough						
No	1153 (36.8)	1983 (63.2)	1	0.000	1	**0.028**
Yes	881 (63.8)	501 (36.2)	2.49 (2.19 to 2.83)		1.29 (1.03 to 1.61)	
Non-productive cough						
No	1701 (55.1)	1384 (44.9)	1	0.000	1	**0.000**
Yes	333 (23.2)	1100 (76.8)	0.35 (0.31 to 0.41)		0.33 (0.26 to 0.41)	
Sore throat						
No	1055 (44.8)	1300 (55.2)	1	0.099	1	**0.000**
Yes	979 (45.3)	1184 (54.7)	1.10 (0.98 to 1.23)		0.64 (0.53 to 0.78)	
Rhinorrhoea						
No	1530 (53.8)	1312 (46.2)	1	0.000	1	**0.000**
Yes	504 (30.1)	1172 (69.9)	0.41 (0.36 to 0.47)		0.28 (0.23 to 0.36)	
Otalgia						
No	1795 (43.7)	2315 (56.3)	1	0.000	1	**0.043**
Yes	239 (58.6)	169 (41.4)	1.62 (1.34 to 1.97)		1.33 (1.01 to 1.76)	
Tender cervical nodes						
No	1777 (42.6)	2397 (57.4)	1	0.000	1	**0.000**
Yes	257 (74.7)	87 (25.3)	4.08 (3.22 to 5.16)		2.19 (1.57 to 3.05)	
Dyspnoea						
No	1908 (44.8)	2350 (55.2)	1	0.001	1	**0.003**
Yes	126 (48.5)	134 (51.5)	1.51 (1.19 to 1.92)		0.58 (0.41 to 0.83)	
Sibilant rhonchi						
No	1860 (43.7)	2397 (56.3)	1	0.000	–	–
Yes	174 (66.7)	87 (33.3)	1.75 (1.37 to 2.25)			

*n=4518 unless otherwise specified.
†n=4425 in final multivariable population-averaged panel-data model using generalised estimating equations which was also adjusted for GP sex, GP age, regular client, antibiotics requested, patient age and smoking status.
‡Wald test; p values highlighted bold indicate independent variables statistically significant at p<0.05; '–' predictor excluded from model.
AB, antibiotic; GP, general practitioner.

confirm this association.[20] In our study however, despite GPs experiencing rather high daily patient loads, this did not influence their antibiotic prescription.

Similar to Akkerman *et al*,[21] more years of GP experience were associated with increased antibiotic treatment. In contrast, an Italian study concluded the opposite, although the antibiotic prescribing of both GPs and paediatricians in children was investigated.[22] Although we did not investigate years of GP practice specifically due to collinearity issues, we found a positive association between GP age and antibiotic prescription, which reflects the GPs' years of practice. In Malta, family medicine was recognised as a specialty in 2004, after which doctors were legally required to undergo specialist training in family medicine. Through the 'grandfather clause', doctors who started training in Malta before November 2003 were eligible to acquire specialisation under certain criteria, essentially exempting them from specialist training.[23] Lower antibiotic prescribing among younger GPs could be explained by the fact that they have more recently undergone specialist training. Older GPs may engage in more habitual behaviour and be in greater need of refresher courses and information on the latest antibiotic prescription guidelines.

Although it is well established that male and female physicians engage in different interaction and communication styles with patients,[24] few studies have investigated the association between GP sex and antibiotic prescribing. Two recent studies investigating antibiotic prescription for aRTCs specifically, found that female GPs prescribe fewer antibiotics[25] particularly to female patients,[26] although the results were not statistically significant. Conversely, our findings revealed that female GPs in Malta are more likely to prescribe antibiotics. Although our sample is representative of the population for sex, we believe that further research is needed to explore and better explain this association.

In our study, antibiotic treatment increased significantly with age, with the elderly (≥65 years) most likely to receive a prescription. The age range of patients included in similar studies varies widely, with most only looking at patient subsets, making it difficult to compare findings on age. While we share similar results as studies carried out in Holland and Australia,[27 28] in England/Wales and Sweden, high rates of antibiotic treatment were found among the elderly and children alike.[29 30] In contrast, in Norway, it was found that patients aged 80 and over actually had the lowest odds of receiving an antibiotic prescription, followed by children younger than 6 years.[20] Given that young children are more likely to visit their paediatrician in Malta, it is possible that more severe cases were missed in this study and that the youngest age groups are under-represented. The higher prescription rates among the elderly in Malta could suggest an augmented concern for their vulnerability towards severe infections, and an understanding that aRTCs in children are likely viral in origin.

Similar to other studies,[31–33] being a current smoker was identified as an independent predictor of antibiotic prescribing. Doctors may feel that smokers will deteriorate without antibiotics, however, there is no evidence that antibiotics provide smokers greater clinical benefit or faster recovery.[32] Fever, productive cough, otalgia or tender cervical nodes were also found to be independent predictors of antibiotic prescribing. Conversely, presenting with a sore throat, non-productive cough, rhinorrhoea or dyspnoea led to a decreased likelihood of prescription. Fever is frequently reported as a significant predictor of antibiotic prescription.[33–35] An Italian study investigating antibiotic prescription in young children, similarly found that otalgia, cervical adenopathy or absence of rhinorrhoea among others were associated with antibiotic prescription.[35] GPs could believe that certain clinical findings, that are often positively associated to prescription, indicate a bacterial infection or are a precursor for more serious illness.

Differentiating between bacterial and viral aetiologies based on signs and/or symptoms alone is challenging and a likely driver of antibiotic overprescription. Although some symptoms suggest a possible bacterial infection and could warrant further investigation, most uncomplicated viral respiratory tract infections last between 5 and 7 days and peak in severity at days 3–6.[36] Given that most patients in this study presented within 3 symptomatic days, some may have benefited from a wait and see approach or delayed prescription, without negative consequences. In fact, a study which examined antibiotic prescribing for acute cough and its impact on recovery across 13 European countries found similar recovery rates in patients prescribed and not prescribed antibiotics.[37] The potential role individual symptoms play in inappropriate antibiotic use should not be overlooked, as it has been indicated that Maltese respondents take antibiotics primarily to treat symptoms as opposed to illnesses.[16]

Being a regular client also contributed to increased likelihood of antibiotic prescribing in this study. Given the structure of primary healthcare in Malta, private sector GPs, who simultaneously compete for business and whose patients pay out-of-pocket, may be eager to please. In fact, research suggests that a trade-off may exist between prudent antibiotic use and cultivating a positive doctor–patient relationship.[38] This is also impacted by expectations and studies have shown that both doctors' belief that a patient expects antibiotics, and patients' actual expectations for antibiotics are associated with antibiotic prescription.[39–41] Requesting antibiotics was an important predictor of antibiotic prescription in our study. While some studies have shown that providing an antibiotic prescription to such patients increased patient satisfaction,[38 39] others suggest that it does not, indicating instead that receiving information when an antibiotic is expected but not needed is as important as receiving a prescription.[42] While it is imperative to understand why patients expect antibiotics and what determines patient satisfaction in Malta, GPs need to find alternative strategies to ensure patient satisfaction without providing an unwarranted antibiotic prescription. One strategy is enhancing doctor–patient communication through communication skills training. Effective communication together with information tools could facilitate decision-making and empower doctors to decline antibiotic requests when unnecessary.[43] This is important, as receiving an antibiotic, particularly when expected, reinforces patients' desire for prescriptions and their perception that they should consult a GP for a similar problem in the future.[44]

A study carried out in Spain also showed that having access to point-of-care tests (rapid antigen detection tests and C reactive protein) was associated with an 18.9% lower antibiotic prescription rate among antibiotic-requesting patients.[45] Having access to rapid tests could help GPs to support their decision not to prescribe by reducing uncertainty thereby lessening the risk that they give in to patient demand, while providing reassurance to patients.[45 46] In Malta, point-of-care tests are largely unavailable, which may augment diagnostic uncertainty. Coupled with patient demand for antibiotics, this exerts prescribing pressure on GPs and may result in an unnecessary prescription. Malta possesses a culture that scores high for uncertainty avoidance, a cultural dimension that has consistently been reported as a potent driver for unnecessary antibiotic use.[14 15 47] Efforts should be made to make low-cost, rapid diagnostics more readily available since these could reduce diagnostic uncertainty and lessen the pressure to prescribe an empiric antibiotic. However, their introduction must be approached with caution to avoid introducing new elements of uncertainty, addressing system factors such as the out-of-pocket cost of tests on the overall consultation, combined with training and support to encourage acceptance. Likewise, patients should be informed about the possibility of low-cost testing to avoid unnecessary antibiotic consumption, thereby safeguarding themselves and their future.

Strengths and limitations

Knowledge on the drivers of antibiotic prescribing in southern European countries with high antibiotic consumption rates is largely lacking, limiting our ability to develop targeted interventions. A first of its kind in Malta, this study paves the way for more research on antibiotic prescribing for aRTCs and other indications in the outpatient sector. The sample of 4518 aRTC cases was sufficient to analyse a large number of potential explanatory variables in multivariable analysis. Data collection tools were adapted from materials used in previous research[48 49] and piloted in the Maltese context. Through user-friendly surveillance forms, we acquired data on provider, patient, consultation and clinical factors which could impact antibiotic prescribing, allowing for deeper analysis of potential influencing factors compared with studies that only examine a subset of these characteristics. The simple to complete forms were intended to aid documentation of as many aRTC cases as possible, while reducing GP drop-outs and non-reporting. Given its design and incorporation into clinical practice, it may have helped reduce the effect of observation bias.[10]

Still, this study does have limitations. Since GPs participated voluntarily, it is possible that participants were more interested in the research area or more conservative prescribers than non-participating GPs. Therefore, our GP sample may not be representative of all Maltese GPs. The audit-based nature of the study may have resulted in measurement error; it is possible that GPs completed patient background information that was atypical to ask during a normal consultation without directly asking the patient. It is also possible that variables of interest located at the end of the surveillance sheet were left unmarked and inaccurately assumed to be non-cases. Lastly, GPs were issued 3 monthly feedback reports and since audit and feedback is a behavioural change intervention in itself it is possible that the antibiotic prescribing rate was affected as a result. However, prior research on the association between surveillance participation and GPs' antibiotic prescription patterns has produced mixed results; a recent randomised control trial reported no effect.[50]

CONCLUSION AND IMPLICATIONS FOR RESEARCH AND POLICY

Our study sheds light on key drivers of community-level antibiotic prescribing for aRTCs in Malta, providing missing scientific evidence necessary to develop tailored interventions aimed at improving prudent antibiotic use. Furthermore, we believe that our study could help guide antimicrobial stewardship initiatives in the community in countries with similar sociocultural traits.

Addressing inappropriate antibiotic prescribing in primary care requires multifaceted interventions that focus on educating providers and patients alike, while providing them with the tools required to ensure that antibiotics are prescribed appropriately and taken only when necessary. Although more experienced GPs could benefit from targeted antibiotic stewardship activities, ongoing continuing medical education initiatives for all GPs are important to ensure that appropriate antibiotic prescription practices are maintained. Communication training in particular is needed to facilitate decision-making and empower doctors to decline antibiotic requests. National antibiotic guidelines should include other diagnostic criteria such as smoking status and better promote the use of delayed antibiotic prescription, particularly in high-prescription contexts. Finally, in settings with high uncertainty avoidance, improving access to low-cost, rapid tests could prove beneficial in supporting GPs' prescribing decisions.

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Contributors EASG, CSL and MAB were involved in the conception of the research study and design of the surveillance data collection sheet. EASG carried out all data collection and was responsible for data management throughout the study's duration. This included maintaining contact with all GPs and overseeing the writing of feedback reports which were subsequently distributed by EASG. EASG and ADH cleaned the dataset. EASG ran statistical analyses with input from ADH and NO. EASG was responsible for drafting the manuscript. EASG, ADH, PZ, NO, MAB and CSL were involved in the interpretation of data and critical revision of the manuscript. EASG produced the final version of the manuscript which was approved by all authors.

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REFERENCES

1. World Health Organization. *Antimicrobial resistance: global report on surveillance*. Geneva: WHO, 2014.
2. Becattini S, Taur Y, Pamer EG. Antibiotic-Induced changes in the intestinal microbiota and disease. *Trends Mol Med* 2016;22:458–78.
3. Goossens H, Ferech M, Vander Stichele R, *et al*. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005;365:579–87.
4. Ababneh MA, Al-Azzam SI, Ababneh R, *et al*. Antibiotic prescribing for acute respiratory infections in children in Jordan. *Int Health* 2017;9:124–30.
5. Saliba-Gustafsson EA, Dunberger Hampton A, Zarb P, *et al*. Antibiotic prescribing for respiratory tract complaints in Malta: a 1 year repeated cross-sectional surveillance study. *J Antimicrob Chemother* 2019;74:1116–24.
6. Bagger K, Nielsen ABS, Siersma V, *et al*. Inappropriate antibiotic prescribing and demand for antibiotics in patients with upper respiratory tract infections is hardly different in female versus male patients as seen in primary care. *Eur J Gen Pract* 2015;21:118–23.
7. Dekker ARJ, Verheij TJM, van der Velden AW. Inappropriate antibiotic prescription for respiratory tract indications: most prominent in adult patients. *Fam Pract* 2015;32:cmv019–7.
8. André M, Odenholt I, Schwan A, *et al*. Upper respiratory tract infections in general practice: diagnosis, antibiotic prescribing, duration of symptoms and use of diagnostic tests. *Scand J Infect Dis* 2002;34:880–6.
9. Aabenhus R, Hansen MP, Saust LT, *et al*. Characterisation of antibiotic prescriptions for acute respiratory tract infections in Danish general practice: a retrospective registry based cohort study. *NPJ Prim Care Respir Med* 2017;27.
10. Cordoba G, Caballero L, Sandholdt H, *et al*. Antibiotic prescriptions for suspected respiratory tract infection in primary care in South America. *J Antimicrob Chemother* 2017;72:305–10.
11. Murphy M, Bradley CP, Byrne S. Antibiotic prescribing in primary care, adherence to guidelines and unnecessary prescribing--an Irish perspective. *BMC Fam Pract* 2012;13:43.
12. McKay R, Mah A, Law MR, *et al*. Systematic review of factors associated with antibiotic prescribing for respiratory tract infections. *Antimicrob Agents Chemother* 2016;60:4106–18.
13. O'Connor R, O'Doherty J, O'Regan A, *et al*. Antibiotic use for acute respiratory tract infections (ARTI) in primary care; what factors affect prescribing and why is it important? A narrative review. *Ir J Med Sci* 2018;187:969–86.
14. Borg MA. National cultural dimensions as drivers of inappropriate ambulatory care consumption of antibiotics in Europe and their relevance to awareness campaigns. *J Antimicrob Chemother* 2012;67:763–7.
15. Deschepper R, Grigoryan L, Lundborg CS, *et al*. Are cultural dimensions relevant for explaining cross-national differences in antibiotic use in Europe? *BMC Health Serv Res* 2008;8:123.
16. TNS Opinion & Social. *Special Eurobarometer 478: antimicrobial resistance*. Brussels: European Commission, 2018.
17. Zarb P, Borg MA. Consumption of antibiotics within ambulatory care in Malta. *Malta Med J* 2011;23:13–18.
18. European Centre for Disease Prevention and Control. Antimicrobial consumption. In: *Annual epidemiological report for 2017*. Stockholm: ECDC, 2018.
19. Saliba-Gustafsson EA, Borg MA, Rosales-Klintz S, *et al*. Maltese antibiotic stewardship programme in the community (MASPIC): protocol of a prospective quasiexperimental social marketing intervention. *BMJ Open* 2017;7:e017992.
20. Gjelstad S, Straand J, Dalen I, *et al*. Do general practitioners' consultation rates influence their prescribing patterns of antibiotics for acute respiratory tract infections? *J Antimicrob Chemother* 2011;66:2425–33.
21. Akkerman AE, Kuyvenhoven MM, van der Wouden JC, *et al*. Prescribing antibiotics for respiratory tract infections by GPs: management and prescriber characteristics. *Br J Gen Pract* 2005;55:114–8.
22. Di Martino M, Lallo A, Kirchmayer U, *et al*. Prevalence of antibiotic prescription in pediatric outpatients in Italy: the role of local health districts and primary care physicians in determining variation. A multilevel design for healthcare decision support. *BMC Public Health* 2017;17:886.
23. Specialist Accreditation Committee Malta. *Minimum criteria for entry to the specialist medical registers*. Malta: Specialist Accreditation Committee Malta, 2006.
24. Roter DL, Hall JA, Aoki Y. Physician gender effects in medical communication: a meta-analytic review. *JAMA* 2002;288:756–64.
25. Rico-Ferreira P, Palazón-Bru A, Calvo-Pérez M, *et al*. Nonadherence to guidelines for prescribing antibiotic therapy to patients with tonsillitis or pharyngotonsillitis: a cross-sectional study. *Curr Med Res Opin* 2015;31:1319–22.
26. Eggermont D, Smit MAM, Kwestroo GA, *et al*. The influence of gender concordance between general practitioner and patient on antibiotic prescribing for sore throat symptoms: a retrospective study. *BMC Fam Pract* 2018;19:175.
27. Haeseker MB, Dukers-Muijrers NHTM, Hoebe CJPA, *et al*. Trends in antibiotic prescribing in adults in Dutch general practice. *PLoS One* 2012;7:e51860.
28. Dallas A, Magin P, Morgan S, *et al*. Antibiotic prescribing for respiratory infections: a cross-sectional analysis of the recent study exploring the habits of early-career doctors in primary care. *Fam Pract* 2015;32:49–55.
29. Majeed A, Moser K. Age- and sex-specific antibiotic prescribing patterns in general practice in England and Wales in 1996. *Br J Gen Pract* 1999;49:735–6.
30. Ternhag A, Grünewald M, Nauclér P, *et al*. Antibiotic consumption in relation to socio-demographic factors, co-morbidity, and accessibility of primary health care. *Scand J Infect Dis* 2014;46:888–96.
31. Shallcross L, Beckley N, Rait G, *et al*. Antibiotic prescribing frequency amongst patients in primary care: a cohort study using electronic health records. *J Antimicrob Chemother* 2017;72:1818–24.
32. Stanton N, Hood K, Kelly MJ, *et al*. Are smokers with acute cough in primary care prescribed antibiotics more often, and to what benefit?

an observational study in 13 European countries. *Eur Respir J* 2010;35:761–7.
33. Manne M, Deshpande A, Hu B, *et al*. Provider variation in antibiotic prescribing and outcomes of respiratory tract infections. *South Med J* 2018;111:235–42.
34. Fischer T, Fischer S, Kochen MM, *et al*. Influence of patient symptoms and physical findings on general practitioners' treatment of respiratory tract infections: a direct observation study. *BMC Fam Pract* 2005;6:6.
35. Moro ML, Marchi M, Gagliotti C, *et al*. Why do paediatricians prescribe antibiotics? results of an Italian regional project. *BMC Pediatr* 2009;9:69.
36. Wald ER, Applegate KE, Bordley C, *et al*. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. *Pediatrics* 2013;132:e262–80.
37. Butler CC, Hood K, Verheij T, *et al*. Variation in antibiotic prescribing and its impact on recovery in patients with acute cough in primary care: prospective study in 13 countries. *BMJ* 2009;338:b2242.
38. Ashworth M, White P, Jongsma H, *et al*. Antibiotic prescribing and patient satisfaction in primary care in England: cross-sectional analysis of national patient survey data and prescribing data. *Br J Gen Pract* 2016;66:e40–6.
39. Coenen S, Francis N, Kelly M, *et al*. Are patient views about antibiotics related to clinician perceptions, management and outcome? A multi-country study in outpatients with acute cough. *PLoS One* 2013;8:e76691.
40. Cockburn J, Pit S. Prescribing behaviour in clinical practice: patients' expectations and doctors' perceptions of patients' expectations--a questionnaire study. *BMJ* 1997;315:520–3.
41. Akkerman AE, Kuyvenhoven MM, van der Wouden JC, *et al*. Determinants of antibiotic overprescribing in respiratory tract infections in general practice. *J Antimicrob Chemother* 2005;56:930–6.
42. Welschen I, Kuyvenhoven M, Hoes A, *et al*. Antibiotics for acute respiratory tract symptoms: patients' expectations, GPs' management and patient satisfaction. *Fam Pract* 2004;21:234–7.
43. Drekonja DM, Filice GA, Greer N, *et al*. Antimicrobial stewardship in outpatient settings: a systematic review. *Infect Control Hosp Epidemiol* 2015;36:142–52.
44. Butler CC, Rollnick S, Kinnersley P, *et al*. Reducing antibiotics for respiratory tract symptoms in primary care: consolidating 'why' and considering 'how'. *Br J Gen Pract* 1998;48:1865–70.
45. Llor C, Bjerrum L, Munck A, *et al*. Access to point-of-care tests reduces the prescription of antibiotics among antibiotic-requesting subjects with respiratory tract infections. *Respir Care* 2014;59:1918–23.
46. Anthierens S, Tonkin-Crine S, Douglas E, *et al*. General practitioners' views on the acceptability and applicability of a web-based intervention to reduce antibiotic prescribing for acute cough in multiple European countries: a qualitative study prior to a randomised trial. *BMC Fam Pract* 2012;13:101.
47. André M, Gröndal H, Strandberg E-L, *et al*. Uncertainty in clinical practice - an interview study with Swedish GPs on patients with sore throat. *BMC Fam Pract* 2016;17:56.
48. Bjerrum L, Munck A, Gahrn-Hansen B, *et al*. Health Alliance for Prudent prescribing, yield and use of antimicrobial drugs in the treatment of respiratory tract infections (happy audit). *BMC Fam Pract* 2010;11:29.
49. André M, Vernby A, Odenholt I, *et al*. Diagnosis-prescribing surveys in 2000, 2002 and 2005 in Swedish general practice: consultations, diagnosis, diagnostics and treatment choices. *Scand J Infect Dis* 2008;40:648–54.
50. Hemkens LG, Saccilotto R, Reyes SL, *et al*. Personalized prescription feedback using routinely collected data to reduce antibiotic use in primary care: a randomized clinical trial. *JAMA Intern Med* 2017;177:176–83.