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

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TITLE PAGE

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

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STRUCTURED ABSTRACT

Objectives: To identify factors which influence general practitioners (GPs') prescription of oral antibiotics for acute respiratory tract complaints (aRTCs) in Malta.

Design: Repeated, cross-sectional surveillance study.

Setting: Maltese general practice; both public sector healthcentres and private sector GP clinics.

Participants: 30 GPs registered on the Malta Medical Council's Specialist Register and 3 GP trainees participated. They registered data of 4831 patients of all ages suffering from any acute respiratory tract complaint. Data were collected monthly between May 2015 and April 2016 during pre-determined 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%. Independent factors positively associated with antibiotic prescribing included female GP sex (95% CI 1.22-4.26), GP age with GPs ≥60 being the most likely (95% CI 14.14-84.98), patient age with patients ≥65 being the most likely (95% CI 1.71-3.18), number of signs and/or symptoms with patients having ≥4 being the most likely (95% CI 5.78-15.99), fever (95% CI 2.08-3.26), productive cough (95% CI 1.03-1.61), otalgia (95% CI 1.01-1.76), tender cervical nodes (95% CI 1.57-3.05), regular clients (95% CI 1.05-1.66), antibiotic requests (95% CI 2.52-8.99) and smoking (95% CI 1.13-1.71). Conversely, patients with non-productive cough (95% CI 0.26-0.41), sore throat

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(95% CI 0.53-0.78), rhinorrhoea (95% CI 0.23-0.36) or dyspnoea (95% CI 0.41-0.83), were less likely to receive an antibiotic prescription.

Conclusions: Antibiotic prescribing for aRTCs was high and influenced but a number of factors. Potentially inappropriate prescribing in primary care can be addressed through multi-faceted interventions addressing modifiable factors associated with prescription.

Trial registration number: NCT03218930

Key words: Primary care, respiratory infections, audit, antibiotic prescribing, general practitioners

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STRENGTHS AND LIMITATIONS

- This is the first study in Malta which 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 aRTC cases as possible, while reducing GP dropouts and non-reporting. Given its design and incorporation into clinical practice, it may have helped reduce the effect of observation bias.
- GPs participation was voluntarily therefore it is possible that the GP sample consists of 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 that variables located at the end of the surveillance sheet were left unmarked and inaccurately assumed to be non-cases.
- Since GPs were issued three-monthly feedback reports, a behaviour change intervention itself, their antibiotic prescribing rate may have been affected as a result of it.

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INTRODUCTION

Since antibiotics were discovered they have saved lives and reduced suffering however their considerable overuse and misuse has, in part, led to the development of antibiotic resistance (ABR), threatening their effectiveness globally. Unchecked, ABR 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 to 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 (RTIs) being the most common diagnoses.[3] Studies have shown that up to 78% of patients are prescribed antibiotics for RTIs 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 ABR is to improve antibiotic use in primary care, particularly among general practitioners (GPs).

While primary care guidelines often recommend limited antibiotic use in RTI treatment, substantial variation exists in practical case management across countries and the evidence of over-prescribing 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

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misdiagnosing and misclassifying the aetiology of RTIs, and may prescribe antibiotics to be on the safe side.

In the latest Special Eurobarometer surveys on antibiotic resistance held in 2013 and 2016, Malta reported the highest antibiotic consumption in Europe with 48% of Maltese respondents reporting taking at least one antibiotic course in a calendar year.[16,17] Non-prescribed use was minimal at <4%.[16,17] Our recently published surveillance study showed that, in 2015/16, 46% of patients with acute respiratory tract complaints (aRTCs) were prescribed antibiotics by their GP.[5] Nation-wide data on antibiotic prescribing in Maltese primary care is lacking and Malta has only been able to provide 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 which impact antibiotic prescribing. Since the majority of Maltese antibiotic consumption occurs in the community and is primarily broad-spectrum,[5,18,19] it is essential to identify and understand the drivers of antibiotic prescribing in primary care to develop targeted antibiotic stewardship activities, improving their chance of success. This study aimed to identify factors which influence GPs' prescription of oral antibiotics 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 quasiexperimental 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 been published.[20] A description of GPs' antibiotic prescribing patterns at baseline has also 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

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responded, of which 35 agreed to participate. Prior to surveillance initiation, two 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 (Figure S1). GPs registered patients seen for aRTCs during 12 pre-determined surveillance weeks (1 week/month without substitutions) between May 2015 and April 2016. Forms were filled by GPs themselves during first consultations with patients of all ages suffering from any aRTC (defined as lower- and upper-RTIs, allergies and exacerbation of COPD/asthma/bronchitis), and included information on patient and clinical factors, clinical assessment, diagnosis and prescribed medicines (Figure S2). 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 three 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 four times during the year, to provide encouragement and address queries. Moreover, GPs received three-monthly individual- and aggregate-level feedback reports on their prescribing patterns.

Eligibility criteria

Only cases diagnosed with an aRTC were included in this study. Cases had to have been consulting with the registering GP for the first time for that presenting complaint. Any follow-

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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. Following data cleaning 313 aRTC cases were subsequently excluded from analysis, reducing our final sample size to 4518.

Statistical analysis

Data were analysed using Microsoft® Excel 2010 and Stata/IC® 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 prescriptions, the latter to be dispensed if symptoms persisted, typically after 48 to 72 hours. It did not include 'delayed instruction', i.e. directions to follow-up for a prescription if symptoms persisted or worsened.

To control for clustering at GP level, potential predictors of antibiotic prescription were assessed using population averaged models using generalised estimating equations (GEE). 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 multi-level categorical variables to test the hypothesis of the overall association.

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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 whilst 20 (61%) worked in the private sector (including private pharmacy clinics). Two (6%) worked in both sectors. 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 Table S2.

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

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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 >38.5ºC, 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 1.22-4.26) and, compared to younger GPs aged between 28 and 39 years, GPs aged 50 to 59 (OR=2.1, 95% CI 1.19-3.77) or 60 years and older (OR=34.7, 95% CI 14.14-84.98) 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 1.71-3.18). 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 5.78-15.99). Additionally, patients with fever >38.5ºC (OR=2.6, 95% CI 2.08-3.26), productive cough (OR=1.3, 95% CI 1.03-1.61), otalgia (OR=1.3, 95% CI 1.01-1.76), tender cervical nodes (OR=2.2, 95% CI 1.57-3.05), regular clients (OR=1.3, 95% CI 1.05-1.66), patients who requested antibiotics (OR=4.8, 95% CI 2.52-8.99) and smokers (OR=1.4, 95% CI 1.13-1.71), were also more likely to be prescribed an antibiotic. Finally, patients with non-productive cough (OR=0.3, 95% CI 0.26-0.41), sore throat (OR=0.6, 95% CI 0.53-0.78), rhinorrhoea (OR=0.3, 95% CI 0.23-0.36) or dyspnoea (OR=0.6, 95% CI 0.41-0.83), 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

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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. Similar to Akkerman et al.,[21] more years of GP experience was 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.

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,[24,25] in England/Wales and Sweden, high rates of antibiotic treatment were found among the elderly and children alike.[26,27] 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 underrepresented. The higher prescription rates among the

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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,[28–30] 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.[29] 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 lead to a decreased likelihood of prescription. Fever is frequently reported as a significant predictor of antibiotic prescription.[30–32] 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.[32] 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 over-prescription. Although some symptoms suggest a possible bacterial infection and could warrant further investigation, most uncomplicated viral RTIs last 5 to 7 days and peak in severity at days 3 to 6.[33] Given that most patients in this study presented within three symptomatic days, some may have benefitted 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.[34] The potential role individual symptoms play in inappropriate antibiotic use should not be overlooked, as an EU-study indicated that Maltese respondents take antibiotics primarily to treat symptoms as opposed to illnesses.[17]

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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.[35] 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.[36–38] Requesting antibiotics was an important predictor of antibiotic prescription in our study. Whilst some studies have shown that providing an antibiotic prescription to such patients increased patient satisfaction,[35,36] 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.[39] Whilst 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.[40] 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.[41]

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.[42] Having access to rapid tests could help GPs support their decision not to prescribe by reducing uncertainty thereby lessening the risk that they give in to patient demand, whilst providing reassurance to patients.[42,43] In Malta, point-of-care tests are largely unavailable, which may augment diagnostic uncertainty.

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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.[14,15,44] 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 RTCs 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[45,46] 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 to 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 dropouts and non-reporting. Given its design and incorporation into clinical practice, it may have helped reduce the effect of observation bias.[10]

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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 three-monthly feedback reports and since audit and feedback is a behaviour change intervention in itself it is possible that the antibiotic prescribing rate has been affected as a result of it. 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.[47]

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, whilst 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

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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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AUTHORS' CONTRIBUTIONS

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 AD cleaned the dataset. EASG ran statistical analyses with input from AD and NO. EASG was responsible for drafting the manuscript. All authors 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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COMPETING INTERESTS

None declared.

ETHICAL APPROVAL

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The University of Malta Research Ethics Committee granted ethical approval and research was conducted in accordance with the Declaration of Helsinki. GP participation was voluntary and informed consent was obtained. GPs could terminate participation at any time, for any reason, without consequence. GP identities were masked using randomly assigned unique identification codes and no personal information was made public. Finally, all patient data collected by GPs was non-identifiable.

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TABLES AND FIGURES (1)

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	aOR (95% CI)	*p*-value
GP sex	male	1,666	(45.1)	2,028	(54.9)	1	0.762	1	**0.010**
	female	368	(44.7)	456	(55.3)	1.10 (0.58-2.10)		2.28 (1.22-4.26)	
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 (1.05-3.70)		1.45 (0.71-2.96)	
	50-59	1,018	(47.5)	1,125	(52.5)	2.53 (1.42-4.51)		2.12 (1.19-3.77)	
	≥60	334	(80.5)	81	(19.5)	9.57 (3.78-24.21)		34.67 (14.14-84.98)	
Years of practice as a GP (n=4,502)	<10	183	(23.7)	589	(76.3)	1	0.026#	–	–
	10-19	301	(40.3)	446	(59.7)	1.77 (0.73-4.32)			
	20-29	1,051	(49.5)	1,074	(50.5)	2.81 (1.34-5.92)			
	≥30	494	(57.6)	364	(42.4)	3.05 (1.32-7.05)			
Total no. of patients examined per day (n=4,436)	<22	1,090	(49.0)	1,135	(51.0)	1	0.488	–	–
	≥22	913	(41.3)	1,298	(58.7)	0.95 (0.83-1.09)			
Type of employment	full-time	1,437	(42.2)	1,966	(57.8)	1	0.217	–	–
	part-time	597	(53.5)	518	(46.5)	1.45 (0.80-2.60)			
Type of practice¶	group	643	(39.5)	987	(60.5)	1	0.062	–	–
	solo	1,391	(48.2)	1,497	(51.8)	1.73 (0.97-3.08)			
Location of GP practice	public healthcentre clinic	318	(34.2)	611	(65.8)	1	0.063#	–	–
	private GP clinic	897	(46.1)	1,050	(53.9)	1.98 (0.97-4.01)			
	private pharmacy clinic	819	(49.9)	823	(50.1)	2.27 (1.10-4.68)			
Location of consultation (n=4,263)	clinic	1,428	(44.8)	1,759	(55.2)	1	0.016	–	–
	home	466	(43.3)	610	(56.7)	1.20 (1.03-1.38)			
Regular client	no	991	(38.9)	1,558	(61.1)	1	0.021	1	**0.016**
	yes	1,043	(53.0)	926	(47.0)	1.23 (1.03-1.48)		1.32 (1.05-1.66)	
Antibiotics requested	no	1,983	(44.6)	2,459	(55.4)	1	0.000	1	**0.000**
	yes	51	(67.1)	25	(32.9)	2.46 (1.57-3.86)		4.76 (2.52-8.99)	

NOTE. *n=4,518 unless otherwise specified; **n=4,425 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; ¶GPs working in public sector healthcentres were defined as group practice practitioners; AB - antibiotic; aOR - adjusted odds ratio; CI - confidence interval; GP - general practitioner; OR - odds ratio; #Wald test; *p*-values highlighted bold indicate independent variables statistically significant at p<0.05; '–' predictor excluded from model

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TABLES AND FIGURES (2)

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	aOR (95% CI)	*p*-value
Sex (n=4,508)	male	910	(43.1)	1,203	(56.9)	1	0.037	–	–
	female	1,118	(46.7)	1,277	(53.3)	1.12 (1.01-1.25)			
Age (years) (n=4,511)	<5	194	(35.7)	350	(64.3)	1	0.000#	1	**0.000#**
	5-11	247	(43.3)	324	(56.7)	1.37 (1.09-1.72)		1.55 (1.15-2.08)	
	12-17	164	(5.9)	193	(54.1)	1.40 (1.08-1.80)		1.74 (1.24-2.44)	
	18-24	215	(46.0)	252	(54.0)	1.47 (1.16-1.87)		1.71 (1.24-2.36)	
	25-44	586	(45.6)	699	(54.4)	1.61 (1.33-1.96)		1.82 (1.40-2.37)	
	45-64	367	(46.5)	423	(53.5)	1.56 (1.26-1.92)		1.72 (1.30-2.29)	
	≥65	260	(52.3)	237	(47.7)	1.86 (1.47-2.35)		2.33 (1.71-3.18)	
Educational level (n=4,484)	pre-school	181	(36.5)	315	(63.5)	1	0.002#	–	–
	primary	327	(43.5)	424	(56.5)	1.23 (0.99-1.53)			
	secondary	850	(47.1)	953	(52.9)	1.43 (1.18-1.74)			
	upper-secondary	351	(45.2)	425	(54.8)	1.38 (1.11-1.71)			
	tertiary	268	(49.2)	277	(50.8)	1.57 (1.24-1.98)			
	none achieved	46	(40.7)	67	(59.3)	1.20 (0.81-1.79)			
No. of persons per household (n=4,465)	1-2	551	(50.7)	536	(49.3)	1	0.000#	–	–
	3-4	1,131	(42.1)	1,556	(57.9)	0.74 (0.65-0.85)			
	≥5	328	(47.5)	363	(52.5)	0.91 (0.76-1.09)			
Contact with children <5 years (n=4,481)	no	1,290	(44.8)	1,591	(55.2)	1	0.198	–	–
	yes	727	(45.4)	873	(54.6)	0.93 (0.82-1.04)			
Current smoker (n=4,453)	no	1,614	(43.4)	2,104	(56.6)	1	0.000	1	**0.002**
	yes	402	(54.7)	333	(45.3)	1.64 (1.42-1.91)		1.39 (1.13-1.71)	

NOTE. *n=4,518 unless otherwise specified; **n=4,425 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; AB - antibiotic; aOR - adjusted odds ratio; CI - confidence interval; OR - odds ratio; #Wald test; *p*-values highlighted bold indicate independent variables statistically significant at p<0.05; '–' predictor excluded from model

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TABLES AND FIGURES (3)

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	aOR (95% CI)	*p*-value
Comorbidities (n=4,218)	no	1,473	(44.5)	1,834	(55.5)	1	0.004	–	–
	yes	442	(48.5)	469	(51.5)	1.23 (1.07-1.41)			
Duration of symptoms (days) (n=4,470)	<1	135	(35.3)	248	(64.7)	1	0.160#	–	–
	1-3	1,369	(46.4)	1,581	(53.6)	1.26 (1.02-1.55)			
	4-7	362	(45.0)	443	(55.0)	1.25 (0.98-1.59)			
	≥8	144	(43.4)	188	(56.6)	1.34 (1.01-1.78)			
No. of signs and symptoms (n=4,497)	1	405	(37.1)	687	(62.9)	1	0.000#	1	**0.000**
	2	700	(39.8)	1,060	(60.2)	2.25 (1.90-2.68)		2.89 (2.26-3.69)	
	3	591	(51.1)	565	(48.9)	4.15 (3.42-5.03)		6.72 (4.73-9.55)	
	≥4	331	(67.7)	158	(32.3)	6.32 (4.97-8.02)		9.62 (5.78-15.99)	
Fever (>38.5°C)	no	1,070	(33.4)	2,138	(66.6)	1	0.000	1	**0.000**
	yes	964	(73.6)	346	(26.4)	4.74 (4.12-5.45)		2.60 (2.08-3.26)	
Productive cough	no	1,153	(36.8)	1,983	(63.2)	1	0.000	1	**0.028**
	yes	881	(63.8)	501	(36.2)	2.49 (2.19-2.83)		1.29 (1.03-1.61)	
Non-productive cough	no	1,701	(55.1)	1,384	(44.9)	1	0.000	1	**0.000**
	yes	333	(23.2)	1,100	(76.8)	0.35 (0.31-0.41)		0.33 (0.26-0.41)	
Sore throat	no	1,055	(44.8)	1,300	(55.2)	1	0.099	1	**0.000**
	yes	979	(45.3)	1,184	(54.7)	1.10 (0.98-1.23)		0.64 (0.53-0.78)	
Rhinorrhoea	no	1,530	(53.8)	1,312	(46.2)	1	0.000	1	**0.000**
	yes	504	(30.1)	1,172	(69.9)	0.41 (0.36-0.47)		0.28 (0.23-0.36)	
Otalgia	no	1,795	(43.7)	2,315	(56.3)	1	0.000	1	**0.043**
	yes	239	(58.6)	169	(41.4)	1.62 (1.34-1.97)		1.33 (1.01-1.76)	
Tender cervical nodes	no	1,777	(42.6)	2,397	(57.4)	1	0.000	1	**0.000**
	yes	257	(74.7)	87	(25.3)	4.08 (3.22-5.16)		2.19 (1.57-3.05)	
Dyspnoea	no	1,908	(44.8)	2,350	(55.2)	1	0.001	1	**0.003**
	yes	126	(48.5)	134	(51.5)	1.51 (1.19-1.92)		0.58 (0.41-0.83)	
Sibilant rhonchi	no	1,860	(43.7)	2,397	(56.3)	1	0.000	–	–
	yes	174	(66.7)	87	(33.3)	1.75 (1.37-2.25)			

NOTE. *n=4,518 unless otherwise specified; **n=4,425 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; AB - antibiotic; aOR - adjusted odds ratio; CI - confidence interval; OR - odds ratio; #Wald test; *p*-values highlighted bold indicate independent variables statistically significant at p<0.05; '–' predictor excluded from model

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SUPPLEMENTARY FILES (1)

GP code *[for office use only]*:

GP demographics

Date: _____

1) Date of birth:			
2) Sex:	☐ Male ☐ Female		
3) Country of birth:			
4) Home address:			
5) E-mail address:			
6a) Telephone no.:		6b) Mobile no.:	
7) Country where you obtained your medical undergrad. degree:			
8) Years of practice as a doctor *(in total)*:			
9a) Year of specialisation in family medicine *(if specialised)*:			
9b) Did you fall under the 'grandfather clause'[1]?		☐ Yes ☐ No	
9c) Are you currently a trainee?		☐ Yes ☐ No	
10) Years of practice as a GP:			
11) How much do you currently work?		☐ Part-time ☐ Full-time	
12) Approximately how many patients do you meet daily?			
13) Health sector of practice *(please tick all relevant options)*:	Type of Sector	Location	
	☐ Public sector	☐ Healthcare centre ☐ Home visits	
	☐ Solo practice	☐ Private clinic ☐ Pharmacy clinic ☐ Home visits	
	☐ Group practice	☐ Private clinic ☐ Pharmacy clinic ☐ Home visits	
	☐ Company doctor		

[1] Being recognised as a fully competent specialist in family medicine, on the basis of acquired experience.

14) Areas within which you conduct home visits *(if applicable)*:	
15) Please write the addresses of your practice/s and tick your main clinic of practice: *(N.B. If you work in a pharmacy, please include the name of that pharmacy)*	
Address	**Main clinic of practice** *(please tick)*
	☐
	☐
	☐
	☐
	☐
	☐
	☐

Thank you for your input!

Figure S1. General practitioner (GP) demographics form

SUPPLEMENTARY FILES (2)

GP code: *[for office use only]*

Date of visit: _____ **Time of visit:** _____

Consultation provided: ☐ at patient's home ☐ at GP clinic ☐ over-the-phone

Patient form for respiratory tract complaints

1. Patient demographics *(please tick all items)*

Age	____ years	
Sex	☐ male	☐ female
Current smoker	☐ yes	☐ no
Other underlying co-morbidities/conditions	☐ yes	☐ no
(E.g. DM, COPD, CHF, immunodeficiency, etc.)	*If yes:* _____	
Patient took antibiotics (past 2 weeks)	☐ yes	☐ no
If yes (antibiotic taken for):	☐ same complaint	☐ other complaint

2. Educational level *(tick only 1 option – highest achieved)*

☐ pre-school/kinder ☐ primary ☐ secondary ☐ upper secondary ☐ tertiary
☐ none of the above

3. Total number of people presently living in the household: _____

4. Regular (daily/several times a week) contact with children <5 years of age

☐ yes ☐ no

5. Total number of symptomatic days *(tick only 1 option)*

☐ <1 ☐ 1-3 ☐ 4-7 ☐ 8-14 ☐ >14

6. Signs and symptoms *(tick at least 1 option)*

☐ fever (>38.5°C) ☐ productive cough ☐ non-productive cough
☐ sore throat (no exudate) ☐ rhinorrhoea ☐ otalgia
☐ purulent otorrhoea ☐ tonsillar exudate ☐ odynophagia
☐ tender cervical nodes ☐ hyperpnoea ☐ dyspnoea
☐ sibilant rhonchi ☐ purulent sputum
☐ other: _____
☐ none of the above

7. Diagnostic tests *(tick at least 1 option)*

Rapid Strep A test		☐ positive	☐ negative		
CRP (mg/L)	☐ <10	☐ 10-24	☐ 25-49	☐ 50-99	☐ >100
Thoracic X-ray		☐ positive	☐ negative		

Other: _____
☐ none of the above

8. Aetiology *(tick only 1 option)*

☐ suspected viral infection ☐ suspected bacterial infection
☐ suspected mixed aetiology

9. Primary clinical diagnosis *(tick only 1 option)*

☐ common cold ☐ acute otitis media ☐ acute sinusitis
☐ acute pharyngitis ☐ acute tonsillitis ☐ acute bronchitis
☐ pneumonia ☐ influenza ☐ allergy
☐ acute exacerbation of chronic bronchitis/COPD/ asthma
☐ suspected TB ☐ other respiratory tract infection: _____

10. Antibiotic therapy *(fill in accordingly)*

Generic name			
Dose/Frequency		Duration	days
Route			

☐ delayed antibiotic prescription ☐ no antibiotics prescribed

11. Symptomatic treatment *(tick at least 1 option)*

☐ analgesic ☐ nasal spray ☐ expectorant ☐ antitussive
☐ decongestant ☐ anti-pyretic ☐ herbal remedy ☐ corticosteroids
☐ anti-histamine ☐ other: _____
☐ none of the above

12. Others *(if applicable)*

☐ allergy to penicillin
☐ referred to specialist/hospital
☐ patient/accompanying person asked for antibiotics
☐ sick leave certificate: ____ days
☐ patient is a regular client in my practice
☐ patient is not a Maltese resident
Nationality *(if known)*: _____

Figure S2. Surveillance data collection form used to register cases with an acute respiratory tract complaint

1

SUPPLEMENTARY FILES (3)

2

Table S1. General practitioner (GP) characteristics (n=33)

		n	(%)
Sex	male	24	(72.7)
	female	9	(27.3)
Age (years)	28-39	7	(21.2)
	40-49	9	(27.3)
	50-59	14	(42.4)
	≥60	3	(9.1)
Years of GP practice (n=32)	<10	6	(18.7)
	10-19	5	(15.6)
	20-29	14	(43.8)
	≥30	7	(21.9)
GP trainee	no	30	(90.9)
	yes	3	(9.1)
Type of employment	part-time	11	(33.3)
	full-time	22	(66.7)
Practice location	public healthcentre clinic	13	(39.4)
	private clinic	14	(42.4)
	private pharmacy clinic	11	(33.3)
Type of practice¶	group	16	(48.5)
	solo	17	(51.5)

NOTE. ¶GPs working in public sector healthcentres were defined as group practice practitioners

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SUPPLEMENTARY FILES (4)

Table S2. Sociodemographic and lifestyle characteristics of patients with acute respiratory tract complaints

		n	(%)
Sex (n=4,508)	male	2,113	(46.9)
	female	2,395	(53.1)
Age (years) (n=4,511)	<5	544	(12.1)
	5-11	571	(12.7)
	12-17	357	(7.9)
	18-24	467	(10.3)
	25-44	1,285	(28.5)
	45-64	790	(17.5)
	≥65	497	(11.0)
Educational level (n=4,484)	pre-school	496	(11.1)
	primary	751	(16.7)
	secondary	1,803	(40.2)
	upper-secondary	776	(17.3)
	tertiary	545	(12.2)
	none achieved	113	(2.5)
Household size (persons/household) (n=4,465)	1-2	1,087	(24.3)
	3-4	2,687	(60.2)
	≥5	691	(15.5)
Contact with children <5 years (n=4,481)	no	2,881	(64.3)
	yes	1,600	(35.7)
Current smoker (n=4,453)	no	3,718	(83.5)
	yes	735	(16.5)

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	25-27

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		(*b*) Report category boundaries when continuous variables were categorized	25-27
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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

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TITLE PAGE

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

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Running title: Factors associated with antibiotic prescribing in patients with acute respiratory tract complaints in Malta

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STRUCTURED 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 healthcentres 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 one-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%. Independent factors positively associated with antibiotic prescribing included female GP sex (OR=2.3, 95% CI 1.22-4.26), GP age with GPs ≥60 being the most likely (OR=34.7, 95% CI 14.14-84.98), patient age with patients ≥65 being the most likely (OR=2.3, 95% CI 1.71-3.18), number of signs and/or symptoms with patients having ≥4 being the most likely (OR=9.6, 95% CI 5.78-15.99), fever (OR=2.6, 95% CI 2.08-3.26), productive cough (OR=1.3, 95% CI 1.03-1.61), otalgia (OR=1.3, 95% CI 1.01-1.76), tender cervical nodes (OR=2.2, 95% CI 1.57-3.05), regular clients (OR=1.3, 95% CI 1.05-1.66), antibiotic requests (OR=4.8, 95% CI 2.52-8.99) and smoking (OR=1.4, 95% CI 1.13-1.71). Conversely patients with non-productive cough (OR=0.3, 95% CI 0.26-0.41), sore

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throat (OR=0.6, 95% CI 0.53-0.78), rhinorrhoea (OR=0.3, 95% CI 0.23-0.36) or dyspnoea (OR=0.6, 95% CI 0.41-0.83), 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 multi-faceted interventions addressing modifiable factors associated with prescription.

Trial registration number: NCT03218930

Key words: Primary care, respiratory infections, audit, antibiotic prescribing, general practitioners

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STRENGTHS AND LIMITATIONS

- This is the first study in Malta which 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 aRTC cases as possible, while reducing GP dropouts 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 three-monthly feedback reports, a behaviour change intervention itself, their antibiotic prescribing rate may have been affected as a result.

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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 over-prescribing 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

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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 surveys on antibiotic resistance held in 2013 and 2016, Malta reported the highest antibiotic consumption in Europe with 48% of Maltese respondents reporting taking at least one antibiotic course in a calendar year.[16,17] Non-prescribed use was minimal at <4%.[16,17] Our recently published descriptive study based on surveillance data showed that, in 2015/16, 46% of patients with acute respiratory tract complaints (aRTCs) were prescribed antibiotics by their GP.[5] The majority of antibiotic consumption in Malta does indeed occur in the community and comprises primarily broad-spectrum antibiotics (i.e. tetracyclines, beta-lactam antibacterials, second- and third- generation cephalosporins, macrolides and fluoroquinolones).[5,18,19]

Nation-wide data on antibiotic prescribing in Maltese primary care is lacking and Malta has only been able to provide 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 which 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 2015/16 surveillance data. Therefore this study aimed to identify factors that influence GPs' oral antibiotic prescribing practices 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 quasiexperimental 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

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been published.[20] An in-depth description of GPs' antibiotic prescribing patterns at baseline, using the same surveillance data but with slightly different eligibility criteria, has already 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, two GPs stopped working clinically; therefore, ultimately 30 GPs and three 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 (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 first consultations with patients of all ages suffering from any aRTC (defined as lower and upper respiratory tract infections, allergies and exacerbation of 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.

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Communication was maintained with GPs throughout surveillance. Each surveillance week, GPs received three 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 four times during the year, to provide encouragement and address queries. Moreover, GPs received three-monthly individual- 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® 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 prescriptions, the latter to be dispensed if symptoms persisted, typically after 48 to 72 hours. It did not include 'delayed instruction', i.e. 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 (GEE).

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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 multi-level 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 whilst 20 (61%) worked in the private sector (including private pharmacy clinics). Two (6%) worked in both sectors. 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 Table S2.

Factors associated with antibiotic prescribing

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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^{o}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 1.22-4.26) and, compared to younger GPs aged between 28 and 39 years, GPs aged 50 to 59 (OR=2.1, 95% CI 1.19-3.77) or 60 years and older (OR=34.7, 95% CI 14.14-84.98) 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 1.71-3.18). 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 5.78-15.99). Additionally, patients with fever >38.5^{o}C (OR=2.6, 95% CI 2.08-3.26), productive cough (OR=1.3, 95% CI 1.03-1.61), otalgia (OR=1.3, 95% CI 1.01-1.76), tender cervical nodes (OR=2.2, 95% CI 1.57-3.05), regular clients (OR=1.3, 95% CI 1.05-1.66), patients who requested antibiotics (OR=4.8, 95% CI 2.52-8.99) and smokers (OR=1.4, 95% CI 1.13-1.71), were also more likely to be prescribed an antibiotic. Conversely, patients with

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non-productive cough (OR=0.3, 95% CI 0.26-0.41), sore throat (OR=0.6, 95% CI 0.53-0.78), rhinorrhoea (OR=0.3, 95% CI 0.23-0.36) or dyspnoea (OR=0.6, 95% CI 0.41-0.83), 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 confirm this association.[21] In our study however, despite GPs experiencing rather high daily patient loads, this did not influence their antibiotic prescription.

Similar to Akkerman et al.,[22] more years of GP experience was 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.[23] 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.[24] Lower antibiotic prescribing among younger GPs could be explained by

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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,[25] 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[26] particularly to female patients,[27] 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,[28,29] in England/Wales and Sweden, high rates of antibiotic treatment were found among the elderly and children alike.[30,31] 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.[21] 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 underrepresented. 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,[32–34] being a current smoker was identified as an independent predictor of antibiotic prescribing. Doctors may feel that smokers will deteriorate without

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antibiotics, however there is no evidence that antibiotics provide smokers greater clinical benefit or faster recovery.[33] 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.[34–36] 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.[36] 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 over-prescription. 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 to 6.[37] Given that most patients in this study presented within three symptomatic days, some may have benefitted 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.[38] The potential role individual symptoms play in inappropriate antibiotic use should not be overlooked, as an EU-study indicated that Maltese respondents take antibiotics primarily to treat symptoms as opposed to illnesses.[17]

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

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please. In fact, research suggests that a trade-off may exist between prudent antibiotic use and cultivating a positive doctor-patient relationship.[39] 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.[40–42] Requesting antibiotics was an important predictor of antibiotic prescription in our study. Whilst some studies have shown that providing an antibiotic prescription to such patients increased patient satisfaction,[39,40] 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.[43] Whilst 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.[44] 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.[45]

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.[46] Having access to rapid tests could help GPs support their decision not to prescribe by reducing uncertainty thereby lessening the risk that they give in to patient demand, whilst providing reassurance to patients.[46,47] 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

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driver for unnecessary antibiotic use.[14,15,48] 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[49,50] 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 to 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 dropouts 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

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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 three-monthly feedback reports and since audit and feedback is a behaviour change intervention in itself it is possible that the antibiotic prescribing rate has been affected as a result of it. 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.[51]

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, whilst 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

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access to low-cost, rapid tests could prove beneficial in supporting GPs' prescribing decisions.

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AUTHORS' CONTRIBUTIONS

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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COMPETING INTERESTS

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None declared.

ETHICAL APPROVAL

The University of Malta Research Ethics Committee granted ethical approval and research was conducted in accordance with the Declaration of Helsinki. GP participation was voluntary and informed consent was obtained. GPs could terminate participation at any time, for any reason, without consequence. GP identities were masked using randomly assigned unique identification codes and no personal information was made public. Finally, all patient data collected by GPs was non-identifiable.

DATA AVAILABILITY STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information. No additional data are available.

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TABLES (1)

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	1,666	(45.1)	2,028	(54.9)	1	0.762	1	**0.010**
	female	368	(44.7)	456	(55.3)	1.10 (0.58-2.10)		2.28 (1.22-4.26)	
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 (1.05-3.70)		1.45 (0.71-2.96)	
	50-59	1,018	(47.5)	1,125	(52.5)	2.53 (1.42-4.51)		2.12 (1.19-3.77)	
	≥60	334	(80.5)	81	(19.5)	9.57 (3.78-24.21)		34.67 (14.14-84.98)	
Years of practice as a GP (n=4,502)	<10	183	(23.7)	589	(76.3)	1	0.026#	–	–
	10-19	301	(40.3)	446	(59.7)	1.77 (0.73-4.32)			
	20-29	1,051	(49.5)	1,074	(50.5)	2.81 (1.34-5.92)			
	≥30	494	(57.6)	364	(42.4)	3.05 (1.32-7.05)			
Total no. of patients examined per day (n=4,436)	<22	1,090	(49.0)	1,135	(51.0)	1	0.488	–	–
	≥22	913	(41.3)	1,298	(58.7)	0.95 (0.83-1.09)			
Type of employment	full-time	1,437	(42.2)	1,966	(57.8)	1	0.217	–	–
	part-time	597	(53.5)	518	(46.5)	1.45 (0.80-2.60)			
Type of practice¶	group	643	(39.5)	987	(60.5)	1	0.062	–	–
	solo	1,391	(48.2)	1,497	(51.8)	1.73 (0.97-3.08)			
Location of GP practice	public healthcentre clinic	318	(34.2)	611	(65.8)	1	0.063#	–	–
	private GP clinic	897	(46.1)	1,050	(53.9)	1.98 (0.97-4.01)			
	private pharmacy clinic	819	(49.9)	823	(50.1)	2.27 (1.10-4.68)			
Location of consultation (n=4,263)	clinic	1,428	(44.8)	1,759	(55.2)	1	0.016	–	–
	home	466	(43.3)	610	(56.7)	1.20 (1.03-1.38)			
Regular client	no	991	(38.9)	1,558	(61.1)	1	0.021	1	**0.016**
	yes	1,043	(53.0)	926	(47.0)	1.23 (1.03-1.48)		1.32 (1.05-1.66)	
Antibiotics requested	no	1,983	(44.6)	2,459	(55.4)	1	0.000	1	**0.000**
	yes	51	(67.1)	25	(32.9)	2.46 (1.57-3.86)		4.76 (2.52-8.99)	

NOTE. *n=4,518 unless otherwise specified; **n=4,425 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; ¶GPs working in public sector healthcentres were defined as group practice practitioners; AB - antibiotic; CI - confidence interval; GP - general practitioner; OR - odds ratio; #Wald test; *p*-values highlighted bold indicate independent variables statistically significant at p<0.05; '–' predictor excluded from model

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TABLES (2)

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=4,508)	male	910	(43.1)	1,203	(56.9)	1	0.037	–	–
	female	1,118	(46.7)	1,277	(53.3)	1.12 (1.01-1.25)			
Age (years) (n=4,511)	<5	194	(35.7)	350	(64.3)	1	0.000#	1	**0.000#**
	5-11	247	(43.3)	324	(56.7)	1.37 (1.09-1.72)		1.55 (1.15-2.08)	
	12-17	164	(45.9)	193	(54.1)	1.40 (1.08-1.80)		1.74 (1.24-2.44)	
	18-24	215	(46.0)	252	(54.0)	1.47 (1.16-1.87)		1.71 (1.24-2.36)	
	25-44	586	(45.6)	699	(54.4)	1.61 (1.33-1.96)		1.82 (1.40-2.37)	
	45-64	367	(46.5)	423	(53.5)	1.56 (1.26-1.92)		1.72 (1.30-2.29)	
	≥65	260	(52.3)	237	(47.7)	1.86 (1.47-2.35)		2.33 (1.71-3.18)	
Educational level (n=4,484)	pre-school	181	(36.5)	315	(63.5)	1	0.002#	–	–
	primary	327	(43.5)	424	(56.5)	1.23 (0.99-1.53)			
	secondary	850	(47.1)	953	(52.9)	1.43 (1.18-1.74)			
	upper-secondary	351	(45.2)	425	(54.8)	1.38 (1.11-1.71)			
	tertiary	268	(49.2)	277	(50.8)	1.57 (1.24-1.98)			
	none achieved	46	(40.7)	67	(59.3)	1.20 (0.81-1.79)			
No. of persons per household (n=4,465)	1-2	551	(50.7)	536	(49.3)	1	0.000#	–	–
	3-4	1,131	(42.1)	1,556	(57.9)	0.74 (0.65-0.85)			
	≥5	328	(47.5)	363	(52.5)	0.91 (0.76-1.09)			
Contact with children <5 years (n=4,481)	no	1,290	(44.8)	1,591	(55.2)	1	0.198	–	–
	yes	727	(45.4)	873	(54.6)	0.93 (0.82-1.04)			
Current smoker (n=4,453)	no	1,614	(43.4)	2,104	(56.6)	1	0.000	1	**0.002**
	yes	402	(54.7)	333	(45.3)	1.64 (1.42-1.91)		1.39 (1.13-1.71)	

NOTE. *n=4,518 unless otherwise specified; **n=4,425 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 (>38.5ºC), productive cough, non-productive cough, sore throat, rhinorrhoea, otalgia, tender cervical nodes and dyspnoea; AB - antibiotic; CI - confidence interval; OR - odds ratio; #Wald test; *p*-values highlighted bold indicate independent variables statistically significant at p<0.05; '–' predictor excluded from model

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TABLES (3)

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=4,218)	no	1,473	(44.5)	1,834	(55.5)	1	0.004	–	–
	yes	442	(48.5)	469	(51.5)	1.23 (1.07-1.41)			
Duration of symptoms (days) (n=4,470)	<1	135	(35.3)	248	(64.7)	1	0.160#	–	–
	1-3	1,369	(46.4)	1,581	(53.6)	1.26 (1.02-1.55)			
	4-7	362	(45.0)	443	(55.0)	1.25 (0.98-1.59)			
	≥8	144	(43.4)	188	(56.6)	1.34 (1.01-1.78)			
No. of signs and symptoms (n=4,497)	1	405	(37.1)	687	(62.9)	1	0.000#	1	**0.000**
	2	700	(39.8)	1,060	(60.2)	2.25 (1.90-2.68)		2.89 (2.26-3.69)	
	3	591	(51.1)	565	(48.9)	4.15 (3.42-5.03)		6.72 (4.73-9.55)	
	≥4	331	(67.7)	158	(32.3)	6.32 (4.97-8.02)		9.62 (5.78-15.99)	
Fever (>38.5°C)	no	1,070	(33.4)	2,138	(66.6)	1	0.000	1	**0.000**
	yes	964	(73.6)	346	(26.4)	4.74 (4.12-5.45)		2.60 (2.08-3.26)	
Productive cough	no	1,153	(36.8)	1,983	(63.2)	1	0.000	1	**0.028**
	yes	881	(63.8)	501	(36.2)	2.49 (2.19-2.83)		1.29 (1.03-1.61)	
Non-productive cough	no	1,701	(55.1)	1,384	(44.9)	1	0.000	1	**0.000**
	yes	333	(23.2)	1,100	(76.8)	0.35 (0.31-0.41)		0.33 (0.26-0.41)	
Sore throat	no	1,055	(44.8)	1,300	(55.2)	1	0.099	1	**0.000**
	yes	979	(45.3)	1,184	(54.7)	1.10 (0.98-1.23)		0.64 (0.53-0.78)	
Rhinorrhoea	no	1,530	(53.8)	1,312	(46.2)	1	0.000	1	**0.000**
	yes	504	(30.1)	1,172	(69.9)	0.41 (0.36-0.47)		0.28 (0.23-0.36)	
Otalgia	no	1,795	(43.7)	2,315	(56.3)	1	0.000	1	**0.043**
	yes	239	(58.6)	169	(41.4)	1.62 (1.34-1.97)		1.33 (1.01-1.76)	
Tender cervical nodes	no	1,777	(42.6)	2,397	(57.4)	1	0.000	1	**0.000**
	yes	257	(74.7)	87	(25.3)	4.08 (3.22-5.16)		2.19 (1.57-3.05)	
Dyspnoea	no	1,908	(44.8)	2,350	(55.2)	1	0.001	1	**0.003**
	yes	126	(48.5)	134	(51.5)	1.51 (1.19-1.92)		0.58 (0.41-0.83)	
Sibilant rhonchi	no	1,860	(43.7)	2,397	(56.3)	1	0.000	–	–
	yes	174	(66.7)	87	(33.3)	1.75 (1.37-2.25)			

NOTE. *n=4,518 unless otherwise specified; **n=4,425 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; AB - antibiotic; CI - confidence interval; OR - odds ratio; #Wald test; *p*-values highlighted bold indicate independent variables statistically significant at p<0.05; '–' predictor excluded from model

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SUPPLEMENTARY FILES (1)

GP code *[for office use only]*:

GP demographics

Date: _____

1) Date of birth:			
2) Sex:	☐ Male ☐ Female		
3) Country of birth:			
4) Home address:			
5) E-mail address:			
6a) Telephone no.:		6b) Mobile no.:	
7) Country where you obtained your medical undergrad. degree:			
8) Years of practice as a doctor *(in total)*:			
9a) Year of specialisation in family medicine *(if specialised)*:			
9b) Did you fall under the 'grandfather clause'[1]?		☐ Yes ☐ No	
9c) Are you currently a trainee?		☐ Yes ☐ No	
10) Years of practice as a GP:			
11) How much do you currently work?		☐ Part-time ☐ Full-time	
12) Approximately how many patients do you meet daily?			
13) Health sector of practice *(please tick all relevant options)*:	Type of Sector	Location	
	☐ Public sector	☐ Healthcare centre ☐ Home visits	
	☐ Solo practice	☐ Private clinic ☐ Pharmacy clinic ☐ Home visits	
	☐ Group practice	☐ Private clinic ☐ Pharmacy clinic ☐ Home visits	
	☐ Company doctor		

[1] Being recognised as a fully competent specialist in family medicine, on the basis of acquired experience.

14) Areas within which you conduct home visits *(if applicable)*:	
15) Please write the addresses of your practice/s and tick your main clinic of practice: *(N.B. If you work in a pharmacy, please include the name of that pharmacy)*	
Address	**Main clinic of practice** *(please tick)*
	☐
	☐
	☐
	☐
	☐
	☐
	☐

Thank you for your input!

Figure S1. General practitioner (GP) demographics form

1

SUPPLEMENTARY FILES (2)

2

Table S1. General practitioner (GP) characteristics (n=33)

		n	(%)
Sex	male	24	(72.7)
	female	9	(27.3)
Age (years)	28-39	7	(21.2)
	40-49	9	(27.3)
	50-59	14	(42.4)
	≥60	3	(9.1)
Years of GP practice (n=32)	<10	6	(18.7)
	10-19	5	(15.6)
	20-29	14	(43.8)
	≥30	7	(21.9)
GP trainee	no	30	(90.9)
	yes	3	(9.1)
Type of employment	part-time	11	(33.3)
	full-time	22	(66.7)
Practice location	public healthcentre clinic	13	(39.4)
	private clinic	14	(42.4)
	private pharmacy clinic	11	(33.3)
Type of practice[¶]	group	16	(48.5)
	solo	17	(51.5)

NOTE. [¶]GPs working in public sector healthcentres were defined as group practice practitioners

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SUPPLEMENTARY FILES (3)

Table S2. Sociodemographic and lifestyle characteristics of patients with acute respiratory tract complaints

		n	(%)
Sex (n=4,508)	male	2,113	(46.9)
	female	2,395	(53.1)
Age (years) (n=4,511)	<5	544	(12.1)
	5-11	571	(12.7)
	12-17	357	(7.9)
	18-24	467	(10.3)
	25-44	1,285	(28.5)
	45-64	790	(17.5)
	≥65	497	(11.0)
Educational level (n=4,484)	pre-school	496	(11.1)
	primary	751	(16.7)
	secondary	1,803	(40.2)
	upper-secondary	776	(17.3)
	tertiary	545	(12.2)
	none achieved	113	(2.5)
Household size (persons/household) (n=4,465)	1-2	1,087	(24.3)
	3-4	2,687	(60.2)
	≥5	691	(15.5)
Contact with children <5 years (n=4,481)	no	2,881	(64.3)
	yes	1,600	(35.7)
Current smoker (n=4,453)	no	3,718	(83.5)
	yes	735	(16.5)

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	25-27

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		(*b*) Report category boundaries when continuous variables were categorized	25-27
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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