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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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3 1 **TITLE PAGE**
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6 2 **Factors associated with antibiotic prescribing in patients with acute respiratory tract**
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8 3 **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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3 45 (95% CI 0.53-0.78), rhinorrhoea (95% CI 0.23-0.36) or dyspnoea (95% CI 0.41-0.83), were
4
5 46 less likely to receive an antibiotic prescription.
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8 47 **Conclusions:** Antibiotic prescribing for aRTCs was high and influenced but a number of
9
10 48 factors. Potentially inappropriate prescribing in primary care can be addressed through multi-
11
12 49 faceted interventions addressing modifiable factors associated with prescription.
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15 50 **Trial registration number:** NCT03218930
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18 51 **Key words:** Primary care, respiratory infections, audit, antibiotic prescribing, general
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20 52 practitioners
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23 53 **Word count:** 299/300 words
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54 STRENGTHS AND LIMITATIONS

- 55 • This is the first study in Malta which looks at factors influencing antibiotic prescribing
56 using repeated cross-sectional surveillance data.
- 57 • The simple to complete surveillance forms were intended to aid documentation of as
58 many aRTC cases as possible, while reducing GP dropouts and non-reporting. Given
59 its design and incorporation into clinical practice, it may have helped reduce the effect
60 of observation bias.
- 61 • GPs participation was voluntarily therefore it is possible that the GP sample consists
62 of more interested in the research area or more conservative prescribers than non-
63 participating GPs, affecting the study's representativeness.
- 64 • The audit-based nature of the study may have resulted in measurement error; GPs may
65 have completed patient background information themselves without directly asking
66 the patient and that variables located at the end of the surveillance sheet were left
67 unmarked and inaccurately assumed to be non-cases.
- 68 • Since GPs were issued three-monthly feedback reports, a behaviour change
69 intervention itself, their antibiotic prescribing rate may have been affected as a result
70 of it.

71 INTRODUCTION

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

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

89 While primary care guidelines often recommend limited antibiotic use in RTI treatment,
90 substantial variation exists in practical case management across countries and the evidence of
91 over-prescribing is abundant.^{7,10,11} The decision to prescribe an antibiotic is complex and
92 influenced by a host of interconnected factors including, but not limited to, provider attitudes
93 and characteristics, patient age, comorbidities, signs and symptoms, expectations,
94 environmental and cultural factors.^{10,12-15} Further cloaked by diagnostic uncertainty, GPs risk

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3 95 misdiagnosing and misclassifying the aetiology of RTIs, and may prescribe antibiotics to be
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5 96 on the safe side.

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7 97 In the latest Special Eurobarometer surveys on antibiotic resistance held in 2013 and 2016,
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9 98 Malta reported the highest antibiotic consumption in Europe with 48% of Maltese respondents
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11 99 reporting taking at least one antibiotic course in a calendar year.^{16,17} Non-prescribed use was
12
13 100 minimal at <4%.^{16,17} Our recently published surveillance study showed that, in 2015/16, 46%
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15 101 of patients with acute respiratory tract complaints (aRTCs) were prescribed antibiotics by
16
17 102 their GP.⁵ Nation-wide data on antibiotic prescribing in Maltese primary care is lacking and
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19 103 Malta has only been able to provide ESAC-Net with wholesale distributor data to estimate
20
21 104 community antibiotic use. As a result, it has not been possible to run in-depth analysis to
22
23 105 elucidate factors which impact antibiotic prescribing. Since the majority of Maltese antibiotic
24
25 106 consumption occurs in the community and is primarily broad-spectrum,^{5,18,19} it is essential to
26
27 107 identify and understand the drivers of antibiotic prescribing in primary care to develop
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29 108 targeted antibiotic stewardship activities, improving their chance of success. This study aimed
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31 109 to identify factors which influence GPs' prescription of oral antibiotics for aRTCs in Malta.
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38 110 **METHODS**

39 111 **Study design, setting and participants**

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42 112 This cross-sectional surveillance study provided baseline data for the Maltese Antibiotic
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44 113 Stewardship Programme in the Community (MASPIC) project, a quasiexperimental social
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46 114 marketing intervention aiming to reduce inappropriate antibiotic prescribing in Maltese
47
48 115 primary care. A study protocol with a detailed description of the study setting and design has
49
50 116 been published.²⁰ A description of GPs' antibiotic prescribing patterns at baseline has also
51
52 117 been presented elsewhere.⁵ In brief, this study was carried out in public and private general
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54 118 practices in Malta. A total of 370 GPs registered on the Malta Medical Council's Specialist
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56 119 Register and 34 GP trainees were invited to the study. Seventy registered GPs and GP trainees
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3 120 responded, of which 35 agreed to participate. Prior to surveillance initiation, two GPs stopped
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5 121 working clinically; therefore, ultimately 30 GPs and 3 GP trainees participated.

122 **Patient and public involvement**

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

127 **Data collection**

128 During enrolment, GPs were asked to complete a background information sheet which
129 included information on demographics, training/experience and service delivery organisation
130 (Figure S1). GPs registered patients seen for aRTCs during 12 pre-determined surveillance
131 weeks (1 week/month without substitutions) between May 2015 and April 2016. Forms were
132 filled by GPs themselves during first consultations with patients of all ages suffering from any
133 aRTC (defined as lower- and upper-RTIs, allergies and exacerbation of
134 COPD/asthma/bronchitis), and included information on patient and clinical factors, clinical
135 assessment, diagnosis and prescribed medicines (Figure S2). Data on the total number of
136 patients seen each day, regardless of complaint, were also collected.

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

142 **Eligibility criteria**

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

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2
3 145 up visits recorded were automatically excluded. For the purpose of this analysis, all cases
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5 146 diagnosed with pneumonia were excluded from the dataset. Cases where more than one
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7 147 aetiology and/or diagnosis was provided or who were consulted over the phone, were also
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9 148 excluded from analysis. Following data cleaning 313 aRTC cases were subsequently excluded
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11
12 149 from analysis, reducing our final sample size to 4518.

150 **Statistical analysis**

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

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

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3 169 Potential predictors were included in the multivariable model if significant at $p < 0.2$ at
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5 170 univariable level and excluded if there were issues with collinearity. A predictor was only
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7 171 kept in the multivariable model if it improved the model and its p -value was less than 0.05.
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10 172 Ultimately 4425 aRTC cases were included in the final multivariable model.
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13 173 **RESULTS**

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16 174 In this cohort of aRTC patients, 2034 (45.0%) received an antibiotic prescription, of which
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18 175 333 (16.4%) were delayed.
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21 176 **GP characteristics**

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23 177 Most GPs were male ($n=24$; 73%). Mean age (years) was 49 ± 12 and mean years of GP
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25 178 practice was 23 ± 11 . Eleven (33%) GPs worked exclusively in the public sector whilst 20
26
27 179 (61%) worked in the private sector (including private pharmacy clinics). Two (6%) worked in
28
29 180 both sectors. Table S1 summarises the GP characteristics.
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32 181 **Patient characteristics**

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34 182 Just over half of patients were female ($n=2395$; 53.1%) and the median age was 29 years
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36 183 (IQR=12-48). Over a third had completed up to secondary school education ($n=3050$; 68.0%).
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38 184 Smoking was reported in 735 (16.5%) cases. A summary of the patients' sociodemographic
39
40 185 and lifestyle characteristics is presented in Table S2.
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43 186 **Factors associated with antibiotic prescribing**

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45 187 The univariable and multivariable associations between GP-, practice- and consultation-level
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47 188 factors (Table 1), patient sociodemographic factors (Table 2), clinical factors (Table 3), and
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49 189 antibiotic prescription are described below.
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53 190 Univariable analysis revealed numerous factors associated with antibiotic prescribing. At GP-
54
55 191 level, GP age was identified as an important predictor with GPs aged 60 and older being most
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57 192 likely to prescribe antibiotics. At consultation-level, regular clients and patients who asked for
58
59 193 antibiotics were more likely to receive an antibiotic prescription. Patient sociodemographic
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194 factors associated with antibiotic prescription included female sex, patient age particularly
195 those aged 65 and older and being a smoker. Finally, a number of patient health status factors
196 were significantly associated with antibiotic prescription at univariable level, with the most
197 important being fever $>38.5^{\circ}\text{C}$, tender cervical nodes and total number of signs and/or
198 symptoms with the odds of prescription increasing as the number increased.

199 In the final multivariable model, female GPs were 2.3 times more likely to prescribe
200 antibiotics (95% CI 1.22-4.26) and, compared to younger GPs aged between 28 and 39 years,
201 GPs aged 50 to 59 (OR=2.1, 95% CI 1.19-3.77) or 60 years and older (OR=34.7, 95% CI
202 14.14-84.98) were more likely to prescribe antibiotics. Increasing patient age also increased
203 the likelihood of receiving an antibiotic prescription, with patients aged 65 and older being the
204 most likely to receive a prescription (OR=2.3, 95% CI 1.71-3.18). The more signs and/or
205 symptoms a patient presented with, the more likely they were to be given an antibiotic, with
206 patients having four or more signs and/or symptoms being the most likely (OR=9.6, 95% CI
207 5.78-15.99). Additionally, patients with fever $>38.5^{\circ}\text{C}$ (OR=2.6, 95% CI 2.08-3.26),
208 productive cough (OR=1.3, 95% CI 1.03-1.61), otalgia (OR=1.3, 95% CI 1.01-1.76), tender
209 cervical nodes (OR=2.2, 95% CI 1.57-3.05), regular clients (OR=1.3, 95% CI 1.05-1.66),
210 patients who requested antibiotics (OR=4.8, 95% CI 2.52-8.99) and smokers (OR=1.4, 95%
211 CI 1.13-1.71), were also more likely to be prescribed an antibiotic. Finally, patients with non-
212 productive cough (OR=0.3, 95% CI 0.26-0.41), sore throat (OR=0.6, 95% CI 0.53-0.78),
213 rhinorrhoea (OR=0.3, 95% CI 0.23-0.36) or dyspnoea (OR=0.6, 95% CI 0.41-0.83), were less
214 likely to be given an antibiotic prescription.

215 DISCUSSION

216 This is the first study in Malta that identifies factors associated with antibiotic prescribing for
217 aRTCs in the community, using surveillance data. While univariable analysis revealed
218 numerous factors associated with antibiotic treatment, multivariable analysis identified

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3 219 several independent predictors of antibiotic prescription at different levels – provider, patient,
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5 220 consultation and clinical.
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8 221 Our results pertaining to GP factors both converge and diverge from prior research. Similar to
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10 222 Akkerman et al.,²¹ more years of GP experience was associated with increased antibiotic
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12 223 treatment. In contrast, an Italian study concluded the opposite, although the antibiotic
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14 224 prescribing of both GPs and paediatricians in children was investigated.²² Although we did
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16 225 not investigate years of GP practice specifically due to collinearity issues, we found a positive
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18 226 association between GP age and antibiotic prescription, which reflects the GPs' years of
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20 227 practice. In Malta, family medicine was recognised as a specialty in 2004, after which doctors
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22 228 were legally required to undergo specialist training in family medicine. Through the
23
24 229 'grandfather clause', doctors who started training in Malta before November 2003 were
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26 230 eligible to acquire specialisation under certain criteria, essentially exempting them from
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28 231 specialist training.²³ Lower antibiotic prescribing among younger GPs could be explained by
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30 232 the fact that they have more recently undergone specialist training. Older GPs may engage in
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32 233 more habitual behaviour and be in greater need of refresher courses and information on the
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34 234 latest antibiotic prescription guidelines.
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40 235 In our study, antibiotic treatment increased significantly with age, with the elderly (≥ 65 years)
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42 236 most likely to receive a prescription. The age-range of patients included in similar studies
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44 237 varies widely, with most only looking at patient subsets, making it difficult to compare
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46 238 findings on age. While we share similar results as studies carried out in Holland and
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48 239 Australia,^{24,25} in England/Wales and Sweden, high rates of antibiotic treatment were found
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50 240 among the elderly and children alike.^{26,27} Given that young children are more likely to visit
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52 241 their paediatrician in Malta, it is possible that more severe cases were missed in this study and
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54 242 that the youngest age groups are underrepresented. The higher prescription rates among the
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3 243 elderly in Malta could suggest an augmented concern for their vulnerability towards severe
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5 244 infections, and an understanding that aRTCs in children are likely viral in origin.

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8 245 Similar to other studies,^{28–30} being a current smoker was identified as an independent
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10 246 predictor of antibiotic prescribing. Doctors may feel that smokers will deteriorate without
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12 247 antibiotics, however there is no evidence that antibiotics provide smokers greater clinical
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15 248 benefit or faster recovery.²⁹ Fever, productive cough, otalgia or tender cervical nodes were
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17 249 also found to be independent predictors of antibiotic prescribing. Conversely, presenting with
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19 250 a sore throat, non-productive cough, rhinorrhoea or dyspnoea lead to a decreased likelihood of
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22 251 prescription. Fever is frequently reported as a significant predictor of antibiotic
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24 252 prescription.^{30–32} An Italian study investigating antibiotic prescription in young children,
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26 253 similarly found that otalgia, cervical adenopathy or absence of rhinorrhoea among others were
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28
29 254 associated with antibiotic prescription.³² GPs could believe that certain clinical findings, that
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31 255 are often positively associated to prescription, indicate a bacterial infection or are a precursor
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33 256 for more serious illness.

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36 257 Differentiating between bacterial and viral aetiologies based on signs and/or symptoms alone
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38 258 is challenging and a likely driver of antibiotic over-prescription. Although some symptoms
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40 259 suggest a possible bacterial infection and could warrant further investigation, most
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43 260 uncomplicated viral RTIs last 5 to 7 days and peak in severity at days 3 to 6.³³ Given that
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45 261 most patients in this study presented within three symptomatic days, some may have
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47 262 benefitted from a wait and see approach or delayed prescription, without negative
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50 263 consequences. In fact, a study which examined antibiotic prescribing for acute cough and its
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52 264 impact on recovery across 13 European countries found similar recovery rates in patients
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54 265 prescribed and not prescribed antibiotics.³⁴ The potential role individual symptoms play in
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57 266 inappropriate antibiotic use should not be overlooked, as an EU-study indicated that Maltese
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59 267 respondents take antibiotics primarily to treat symptoms as opposed to illnesses.¹⁷
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3 268 Being a regular client also contributed to increased likelihood of antibiotic prescribing in this
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5 269 study. Given the structure of primary healthcare in Malta, private sector GPs, who
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7 270 simultaneously compete for business and whose patients pay out-of-pocket, may be eager to
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9 271 please. In fact, research suggests that a trade-off may exist between prudent antibiotic use and
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11 272 cultivating a positive doctor-patient relationship.³⁵ This is also impacted by expectations and
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13 273 studies have shown that both doctors' belief that a patient expects antibiotics, and patients'
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15 274 actual expectations for antibiotics are associated with antibiotic prescription.³⁶⁻³⁸ Requesting
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17 275 antibiotics was an important predictor of antibiotic prescription in our study. Whilst some
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19 276 studies have shown that providing an antibiotic prescription to such patients increased patient
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21 277 satisfaction,^{35,36} others suggest that it does not, indicating instead that receiving information
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23 278 when an antibiotic is expected but not needed is as important as receiving a prescription.³⁹
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25 279 Whilst it is imperative to understand why patients expect antibiotics and what determines
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27 280 patient satisfaction in Malta, GPs need to find alternative strategies to ensure patient
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29 281 satisfaction without providing an unwarranted antibiotic prescription. One strategy is
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31 282 enhancing doctor-patient communication through communication skills training. Effective
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33 283 communication together with information tools could facilitate decision-making and empower
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35 284 doctors to decline antibiotic requests when unnecessary.⁴⁰ This is important as receiving an
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37 285 antibiotic, particularly when expected, reinforces patients' desire for prescriptions and their
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39 286 perception that they should consult a GP for a similar problem in the future.⁴¹
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41 287 A study carried out in Spain also showed that having access to point-of-care tests (rapid
42
43 288 antigen detection tests and C-reactive protein) was associated with an 18.9% lower antibiotic
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45 289 prescription rate among antibiotic-requesting patients.⁴² Having access to rapid tests could
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47 290 help GPs support their decision not to prescribe by reducing uncertainty thereby lessening the
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49 291 risk that they give in to patient demand, whilst providing reassurance to patients.^{42,43} In Malta,
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51 292 point-of-care tests are largely unavailable, which may augment diagnostic uncertainty.
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3 293 Coupled with patient demand for antibiotics, this exerts prescribing pressure on GPs and may
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5 294 result in an unnecessary prescription. Malta possesses a culture that scores high for
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7 295 uncertainty avoidance, a cultural dimension that has consistently been reported as a potent
8
9 296 driver for unnecessary antibiotic use.^{14,15,44} Efforts should be made to make low-cost, rapid
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11 297 diagnostics more readily available since these could reduce diagnostic uncertainty and lessen
12
13 298 the pressure to prescribe an empiric antibiotic. However, their introduction must be
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15 299 approached with caution to avoid introducing new elements of uncertainty, addressing system
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17 300 factors such as the out-of-pocket cost of tests on the overall consultation, combined with
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19 301 training and support to encourage acceptance. Likewise, patients should be informed about
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21 302 the possibility of low-cost testing to avoid unnecessary antibiotic consumption, thereby
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23 303 safeguarding themselves and their future.

28 304 **Strengths and limitations**

30 305 Knowledge on the drivers of antibiotic prescribing in southern European countries with high
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32 306 antibiotic consumption rates is largely lacking, limiting our ability to develop targeted
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34 307 interventions. A first of its kind in Malta, this study paves the way for more research on
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36 308 antibiotic prescribing for RTCs and other indications in the outpatient sector. The sample of
37
38 309 4518 aRTC cases was sufficient to analyse a large number of potential explanatory variables
39
40 310 in multivariable analysis. Data collection tools were adapted from materials used in previous
41
42 311 research^{45,46} and piloted in the Maltese context. Through user-friendly surveillance forms, we
43
44 312 acquired data on provider, patient, consultation and clinical factors which could impact
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46 313 antibiotic prescribing, allowing for deeper analysis of potential influencing factors compared
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48 314 to studies that only examine a subset of these characteristics. The simple to complete forms
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50 315 were intended to aid documentation of as many aRTC cases as possible, while reducing GP
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52 316 dropouts and non-reporting. Given its design and incorporation into clinical practice, it may
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54 317 have helped reduce the effect of observation bias.¹⁰
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3 318 Still, this study does have limitations. Since GPs participated voluntarily, it is possible that
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5 319 participants were more interested in the research area or more conservative prescribers than
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7 320 non-participating GPs. Therefore our GP sample may not be representative of all Maltese
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9 321 GPs. The audit-based nature of the study may have resulted in measurement error; it is
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11 322 possible that GPs completed patient background information that was atypical to ask during a
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13 323 normal consultation without directly asking the patient. It is also possible that variables of
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15 324 interest located at the end of the surveillance sheet were left unmarked and inaccurately
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17 325 assumed to be non-cases. Lastly, GPs were issued three-monthly feedback reports and since
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19 326 audit and feedback is a behaviour change intervention in itself it is possible that the antibiotic
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21 327 prescribing rate has been affected as a result of it. However, prior research on the association
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23 328 between surveillance participation and GPs' antibiotic prescription patterns has produced
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25 329 mixed results; a recent randomised control trial reported no effect.⁴⁷
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31 **CONCLUSION AND IMPLICATIONS FOR RESEARCH AND POLICY**

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35 331 Our study sheds light on key drivers of community-level antibiotic prescribing for aRTCs in
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37 332 Malta, providing missing scientific evidence necessary to develop tailored interventions
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39 333 aimed at improving prudent antibiotic use. Furthermore, we believe that our study could help
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41 334 guide antimicrobial stewardship initiatives in the community in countries with similar
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43 335 sociocultural traits.

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46 336 Addressing inappropriate antibiotic prescribing in primary care requires multifaceted
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48 337 interventions that focus on educating providers and patients alike, whilst providing them with
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50 338 the tools required to ensure that antibiotics are prescribed appropriately and taken only when
51
52 339 necessary. Although more experienced GPs could benefit from targeted antibiotic stewardship
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54 340 activities, ongoing continuing medical education initiatives for all GPs are important to ensure
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56 341 that appropriate antibiotic prescription practices are maintained. Communication training in
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58 342 particular is needed to facilitate decision-making and empower doctors to decline antibiotic
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3 343 requests. National antibiotic guidelines should include other diagnostic criteria such as
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5 344 smoking status and better promote the use of delayed antibiotic prescription, particularly in
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7 345 high-prescription contexts. Finally, in settings with high uncertainty avoidance, improving
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10 346 access to low-cost, rapid tests could prove beneficial in supporting GPs' prescribing
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12 347 decisions.
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356 **AUTHORS' CONTRIBUTIONS**

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

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370 **COMPETING INTERESTS**

371 None declared.

372 **ETHICAL APPROVAL**

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3 373 The University of Malta Research Ethics Committee granted ethical approval and research
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5 374 was conducted in accordance with the Declaration of Helsinki. GP participation was voluntary
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7 375 and informed consent was obtained. GPs could terminate participation at any time, for any
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9 376 reason, without consequence. GP identities were masked using randomly assigned unique
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11 377 identification codes and no personal information was made public. Finally, all patient data
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14 378 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)	
	<10	183	(23.7)	589	(76.3)	1	0.026#		
Years of practice as a GP (n=4,502)	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

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

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)			
	1	405	(37.1)	687	(62.9)	1	0.000 [#]	1	0.000
No. of signs and symptoms (n=4,497)	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)	
	no	1,070	(33.4)	2,138	(66.6)	1	0.000	1	0.000
Fever (>38.5°C)	yes	964	(73.6)	346	(26.4)	4.74 (4.12-5.45)		2.60 (2.08-3.26)	
	no	1,153	(36.8)	1,983	(63.2)	1	0.000	1	0.028
Productive cough	yes	881	(63.8)	501	(36.2)	2.49 (2.19-2.83)		1.29 (1.03-1.61)	
	no	1,701	(55.1)	1,384	(44.9)	1	0.000	1	0.000
Non-productive cough	yes	333	(23.2)	1,100	(76.8)	0.35 (0.31-0.41)		0.33 (0.26-0.41)	
	no	1,055	(44.8)	1,300	(55.2)	1	0.099	1	0.000
Sore throat	yes	979	(45.3)	1,184	(54.7)	1.10 (0.98-1.23)		0.64 (0.53-0.78)	
	no	1,530	(53.8)	1,312	(46.2)	1	0.000	1	0.000
Rhinorrhoea	yes	504	(30.1)	1,172	(69.9)	0.41 (0.36-0.47)		0.28 (0.23-0.36)	
	no	1,795	(43.7)	2,315	(56.3)	1	0.000	1	0.043
Otalgia	yes	239	(58.6)	169	(41.4)	1.62 (1.34-1.97)		1.33 (1.01-1.76)	
	no	1,777	(42.6)	2,397	(57.4)	1	0.000	1	0.000
Tender cervical nodes	yes	257	(74.7)	87	(25.3)	4.08 (3.22-5.16)		2.19 (1.57-3.05)	
	no	1,908	(44.8)	2,350	(55.2)	1	0.001	1	0.003
Dyspnoea	yes	126	(48.5)	134	(51.5)	1.51 (1.19-1.92)		0.58 (0.41-0.83)	
	no	1,860	(43.7)	2,397	(56.3)	1	0.000	–	–
Sibilant rhonchi	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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For peer review only

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SUPPLEMENTARY FILES (1)

GP code [for office use only]:

GP demographics

Date: _____

1) Date of birth:		
2) Sex: <input type="checkbox"/> Male <input type="checkbox"/> 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 ?		<input type="checkbox"/> Yes <input type="checkbox"/> No
9c) Are you currently a trainee?		<input type="checkbox"/> Yes <input type="checkbox"/> No
10) Years of practice as a GP:		
11) How much do you currently work? <input type="checkbox"/> Part-time <input type="checkbox"/> 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
	<input type="checkbox"/> Public sector	<input type="checkbox"/> Healthcare centre <input type="checkbox"/> Home visits
	<input type="checkbox"/> Solo practice	<input type="checkbox"/> Private clinic <input type="checkbox"/> Pharmacy clinic <input type="checkbox"/> Home visits
	<input type="checkbox"/> Group practice	<input type="checkbox"/> Private clinic <input type="checkbox"/> Pharmacy clinic <input type="checkbox"/> Home visits
<input type="checkbox"/> Company doctor		

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)
	<input type="checkbox"/>
	<input type="checkbox"/>
	<input type="checkbox"/>
	<input type="checkbox"/>
	<input type="checkbox"/>
	<input type="checkbox"/>
	<input type="checkbox"/>

Thank you for your input!

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

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

<p>1. Patient demographics <i>(please tick all items)</i></p> <p>Age _____ years</p> <p>Sex <input type="checkbox"/> male <input type="checkbox"/> female</p> <p>Current smoker <input type="checkbox"/> yes <input type="checkbox"/> no</p> <p>Other underlying co-morbidities/conditions (E.g. DM, COPD, CHF, immunodeficiency, etc.) <input type="checkbox"/> yes <input type="checkbox"/> no</p> <p><i>If yes:</i> _____</p> <p>Patient took antibiotics (past 2 weeks) <input type="checkbox"/> yes <input type="checkbox"/> no</p> <p><i>If yes (antibiotic taken for):</i> <input type="checkbox"/> same complaint <input type="checkbox"/> other complaint</p> <hr/> <p>2. Educational level <i>(tick only 1 option – highest achieved)</i></p> <p><input type="checkbox"/> pre-school/kinder <input type="checkbox"/> primary <input type="checkbox"/> secondary <input type="checkbox"/> upper secondary <input type="checkbox"/> tertiary</p> <p><input type="checkbox"/> none of the above</p> <hr/> <p>3. Total number of people presently living in the household: _____</p> <hr/> <p>4. Regular (daily/several times a week) contact with children <5 years of age</p> <p><input type="checkbox"/> yes <input type="checkbox"/> no</p> <hr/> <p>5. Total number of symptomatic days <i>(tick only 1 option)</i></p> <p><input type="checkbox"/> <1 <input type="checkbox"/> 1-3 <input type="checkbox"/> 4-7 <input type="checkbox"/> 8-14 <input type="checkbox"/> >14</p> <hr/> <p>6. Signs and symptoms <i>(tick at least 1 option)</i></p> <p><input type="checkbox"/> fever (>38.5°C) <input type="checkbox"/> productive cough <input type="checkbox"/> non-productive cough</p> <p><input type="checkbox"/> sore throat (no exudate) <input type="checkbox"/> rhinorrhoea <input type="checkbox"/> otalgia</p> <p><input type="checkbox"/> purulent otorrhoea <input type="checkbox"/> tonsillar exudate <input type="checkbox"/> odynophagia</p> <p><input type="checkbox"/> tender cervical nodes <input type="checkbox"/> hyperpnoea <input type="checkbox"/> dyspnoea</p> <p><input type="checkbox"/> sibilant rhonchi <input type="checkbox"/> purulent sputum</p> <p><input type="checkbox"/> other: _____</p> <p><input type="checkbox"/> none of the above</p> <hr/> <p>7. Diagnostic tests <i>(tick at least 1 option)</i></p> <p>Rapid Strep A test <input type="checkbox"/> positive <input type="checkbox"/> negative</p> <p>CRP (mg/L) <input type="checkbox"/> <10 <input type="checkbox"/> 10-24 <input type="checkbox"/> 25-49 <input type="checkbox"/> 50-99 <input type="checkbox"/> >100</p> <p>Thoracic X-ray <input type="checkbox"/> positive <input type="checkbox"/> negative</p> <p>Other: _____</p> <p><input type="checkbox"/> none of the above</p>	<p>8. Aetiology <i>(tick only 1 option)</i></p> <p><input type="checkbox"/> suspected viral infection <input type="checkbox"/> suspected bacterial infection</p> <p><input type="checkbox"/> suspected mixed aetiology</p> <hr/> <p>9. Primary clinical diagnosis <i>(tick only 1 option)</i></p> <p><input type="checkbox"/> common cold <input type="checkbox"/> acute otitis media <input type="checkbox"/> acute sinusitis</p> <p><input type="checkbox"/> acute pharyngitis <input type="checkbox"/> acute tonsillitis <input type="checkbox"/> acute bronchitis</p> <p><input type="checkbox"/> pneumonia <input type="checkbox"/> influenza <input type="checkbox"/> allergy</p> <p><input type="checkbox"/> acute exacerbation of chronic bronchitis/COPD/ asthma</p> <p><input type="checkbox"/> suspected TB <input type="checkbox"/> other respiratory tract infection: _____</p> <hr/> <p>10. Antibiotic therapy <i>(fill in accordingly)</i></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Generic name</td> <td colspan="3"></td> </tr> <tr> <td>Dose/Frequency</td> <td style="width: 20%;">Duration</td> <td colspan="2" style="width: 30%;">days</td> </tr> <tr> <td>Route</td> <td colspan="3"></td> </tr> </table> <p><input type="checkbox"/> delayed antibiotic prescription <input type="checkbox"/> no antibiotics prescribed</p> <hr/> <p>11. Symptomatic treatment <i>(tick at least 1 option)</i></p> <p><input type="checkbox"/> analgesic <input type="checkbox"/> nasal spray <input type="checkbox"/> expectorant <input type="checkbox"/> antitussive</p> <p><input type="checkbox"/> decongestant <input type="checkbox"/> anti-pyretic <input type="checkbox"/> herbal remedy <input type="checkbox"/> corticosteroids</p> <p><input type="checkbox"/> anti-histamine <input type="checkbox"/> other: _____</p> <p><input type="checkbox"/> none of the above</p> <hr/> <p>12. Others <i>(if applicable)</i></p> <p><input type="checkbox"/> allergy to penicillin</p> <p><input type="checkbox"/> referred to specialist/hospital</p> <p><input type="checkbox"/> patient/accompanying person asked for antibiotics</p> <p><input type="checkbox"/> sick leave certificate: _____ days</p> <p><input type="checkbox"/> patient is a regular client in my practice</p> <p><input type="checkbox"/> patient is not a Maltese resident</p> <p>Nationality <i>(if known):</i> _____</p>	Generic name				Dose/Frequency	Duration	days		Route			
Generic name													
Dose/Frequency	Duration	days											
Route													

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)
	<10	6	(18.7)
Years of GP practice (n=32)	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

4 SUPPLEMENTARY FILES (4)

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

		n	(%)
7 Sex (n=4,508)	male	2,113	(46.9)
	female	2,395	(53.1)
17 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)
24 Educational level (n=4,484)	≥65	497	(11.0)
	pre-school	496	(11.1)
	primary	751	(16.7)
	secondary	1,803	(40.2)
	upper-secondary	776	(17.3)
	tertiary	545	(12.2)
29 Household size (persons/household) (n=4,465)	none achieved	113	(2.5)
	1-2	1,087	(24.3)
	3-4	2,687	(60.2)
32 Contact with children <5 years (n=4,481)	≥5	691	(15.5)
	no	2,881	(64.3)
34 Current smoker (n=4,453)	yes	1,600	(35.7)
	no	3,718	(83.5)
	yes	735	(16.5)

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

		(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.

BMJ Open

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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Keywords:	PRIMARY CARE, Respiratory infections < THORACIC MEDICINE, AUDIT, Antibiotic prescribing, General practitioners

SCHOLARONE™
Manuscripts

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3 1 **TITLE PAGE**
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6 2 **Factors associated with antibiotic prescribing in patients with acute respiratory tract**
7
8 3 **complaints in Malta: a one-year repeated cross-sectional surveillance study**
9

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45 18 **Running title:** Factors associated with antibiotic prescribing in patients with acute
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47 19 respiratory tract complaints in Malta
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20 **STRUCTURED ABSTRACT**

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

23 **Design:** Repeated, cross-sectional surveillance.

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

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

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

34 **Results:** The antibiotic prescription rate was 45%. Independent factors positively associated
35 with antibiotic prescribing included female GP sex (OR=2.3, 95% CI 1.22-4.26), GP age with
36 GPs ≥ 60 being the most likely (OR=34.7, 95% CI 14.14-84.98), patient age with patients ≥ 65
37 being the most likely (OR=2.3, 95% CI 1.71-3.18), number of signs and/or symptoms with
38 patients having ≥ 4 being the most likely (OR=9.6, 95% CI 5.78-15.99), fever (OR=2.6, 95%
39 CI 2.08-3.26), productive cough (OR=1.3, 95% CI 1.03-1.61), otalgia (OR=1.3, 95% CI 1.01-
40 1.76), tender cervical nodes (OR=2.2, 95% CI 1.57-3.05), regular clients (OR=1.3, 95% CI
41 1.05-1.66), antibiotic requests (OR=4.8, 95% CI 2.52-8.99) and smoking (OR=1.4, 95% CI
42 1.13-1.71). Conversely patients with non-productive cough (OR=0.3, 95% CI 0.26-0.41), sore

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3 43 throat (OR=0.6, 95% CI 0.53-0.78), rhinorrhoea (OR=0.3, 95% CI 0.23-0.36) or dyspnoea
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5 44 (OR=0.6, 95% CI 0.41-0.83), were less likely to receive an antibiotic prescription.
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8 45 **Conclusion:** Antibiotic prescribing for aRTCs was high and influenced by a number of
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10 46 factors. Potentially inappropriate prescribing in primary care can be addressed through multi-
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12 47 faceted interventions addressing modifiable factors associated with prescription.
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15 48 **Trial registration number:** NCT03218930
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18 49 **Key words:** Primary care, respiratory infections, audit, antibiotic prescribing, general
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20 50 practitioners
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51 STRENGTHS AND LIMITATIONS

- 52 • This is the first study in Malta which looks at factors influencing antibiotic prescribing
53 using repeated cross-sectional surveillance data.
- 54 • The simple to complete surveillance forms were intended to aid documentation of as
55 many aRTC cases as possible, while reducing GP dropouts and non-reporting. Given
56 its design and incorporation into clinical practice, it may have helped to reduce the
57 effect of observation bias.
- 58 • GP participation was voluntarily therefore it is possible that the GP sample consists of
59 GPs who were more interested in the research area or more conservative prescribers
60 than non-participating GPs, affecting the study's representativeness.
- 61 • The audit-based nature of the study may have resulted in measurement error; GPs may
62 have completed patient background information themselves without directly asking
63 the patient and variables located at the end of the surveillance sheet that were left
64 unmarked may have been inaccurately assumed to be non-cases.
- 65 • Since GPs were issued three-monthly feedback reports, a behaviour change
66 intervention itself, their antibiotic prescribing rate may have been affected as a result.

67 INTRODUCTION

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

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

85 While primary care guidelines often recommend limited antibiotic use in the treatment of
86 respiratory tract infections, substantial variation exists in practical case management across
87 countries and the evidence of over-prescribing is abundant.^{7,10,11} The decision to prescribe an
88 antibiotic is complex and influenced by a host of interconnected factors including, but not
89 limited to, provider attitudes and characteristics, patient age, comorbidities, signs and
90 symptoms, expectations, environmental and cultural factors.^{10,12-15} Further cloaked by

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3 91 diagnostic uncertainty, GPs risk misdiagnosing and misclassifying the aetiology of respiratory
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5 92 tract infections, and may prescribe antibiotics to be on the safe side.
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8 93 In the latest Special Eurobarometer surveys on antibiotic resistance held in 2013 and 2016,
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10 94 Malta reported the highest antibiotic consumption in Europe with 48% of Maltese respondents
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12 95 reporting taking at least one antibiotic course in a calendar year.^{16,17} Non-prescribed use was
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14 96 minimal at <4%.^{16,17} Our recently published descriptive study based on surveillance data
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17 97 showed that, in 2015/16, 46% of patients with acute respiratory tract complaints (aRTCs)
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19 98 were prescribed antibiotics by their GP.⁵ The majority of antibiotic consumption in Malta
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21 99 does indeed occur in the community and comprises primarily broad-spectrum antibiotics (i.e.
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24 100 tetracyclines, beta-lactam antibacterials, second- and third- generation cephalosporins,
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26 101 macrolides and fluoroquinolones).^{5,18,19}
27
28 102 Nation-wide data on antibiotic prescribing in Maltese primary care is lacking and Malta has
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30 103 only been able to provide ESAC-Net with wholesale distributor data to estimate community
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32 104 antibiotic use. As a result, it has not been possible to run in-depth analysis to elucidate factors
33
34 105 which impact antibiotic prescribing. Recognising the need to identify and understand the
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37 106 drivers of antibiotic prescribing in primary care to develop targeted antibiotic stewardship
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39 107 activities and improve their chance of success, we decided to carry a more in-depth analysis
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42 108 of our 2015/16 surveillance data. Therefore this study aimed to identify factors that influence
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44 109 GPs' oral antibiotic prescribing practices for aRTCs in Malta.
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48 110 **METHODS**

49 50 51 111 **Study design, setting and participants**

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53 112 This cross-sectional surveillance study provided baseline data for the Maltese Antibiotic
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55 113 Stewardship Programme in the Community (MASPIC) project, a quasiexperimental social
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57 114 marketing intervention aiming to reduce inappropriate antibiotic prescribing in Maltese
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59 115 primary care. A study protocol with a detailed description of the study setting and design has
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3 116 been published.²⁰ An in-depth description of GPs' antibiotic prescribing patterns at baseline,
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5 117 using the same surveillance data but with slightly different eligibility criteria, has already
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7 118 been presented elsewhere.⁵
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10 119 In brief, this study was carried out in public and private general practices in Malta. A total of
11
12 120 370 GPs registered on the Malta Medical Council's Specialist Register and 34 GP trainees
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14 121 were invited to the study. Seventy registered GPs and GP trainees responded, of which 35
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16 122 agreed to participate. Prior to surveillance initiation, two GPs stopped working clinically;
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18 123 therefore, ultimately 30 GPs and three GP trainees participated.
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21 124 **Patient and public involvement**

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23 125 This study was conducted without patient or public involvement. Patients were not invited to
24
25 126 comment on the study design and were not consulted to develop patient relevant outcomes or
26
27 127 interpret results. Patients were neither requested to contribute to the writing or editing of this
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29 128 document for readability or accuracy.
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32 129 **Data collection**

33
34 130 During enrolment, GPs were asked to complete a background information sheet which
35
36 131 included information on demographics, training/experience and service delivery organisation
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38 132 (Figure S1). GPs registered patients seen for aRTCs during 12 predetermined surveillance
39
40 133 weeks (1 week/month without substitutions) between May 2015 and April 2016. Forms were
41
42 134 completed by the GPs themselves during first consultations with patients of all ages suffering
43
44 135 from any aRTC (defined as lower and upper respiratory tract infections, allergies and
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46 136 exacerbation of COPD/asthma/bronchitis), and included information on patient and clinical
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48 137 factors, clinical assessment, diagnosis and prescribed medicines. The surveillance data
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50 138 collection form has been published elsewhere.⁵ Data on the total number of patients seen each
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52 139 day, regardless of complaint, were also collected.
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3 140 Communication was maintained with GPs throughout surveillance. Each surveillance week,
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5 141 GPs received three text messages, one to remind them to prepare for data collection, another
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7 142 to initiate it and a third to conclude it. GPs were also contacted by phone at most four times
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9 143 during the year, to provide encouragement and address queries. Moreover, GPs received
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11 144 three-monthly individual- and aggregate-level feedback reports on their prescribing patterns.
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14 145 **Eligibility criteria**

16 146 Only cases diagnosed with an aRTC were included in this study. Cases were only considered
17
18 147 for analysis if they were consulting with the participating GP for the first time for that
19
20 148 presenting complaint. Any follow-up visits recorded were automatically excluded. For the
21
22 149 purpose of this analysis, all cases diagnosed with pneumonia were excluded from the dataset.
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24 150 Cases where more than one aetiology and/or diagnosis was provided or who were consulted
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26 151 over the phone, were also excluded from analysis. As a result 313 aRTC cases were excluded
27
28 152 from analysis following data cleaning, reducing our final sample size to 4518.
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33 153 **Statistical analysis**

35 154 Data were analysed using Microsoft® Excel 2010 and Stata/IC® 13.1. Surveillance items not
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37 155 marked were assumed not present and analysed as absent. Analyses were conducted using
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39 156 complete case analysis. Descriptive statistics were calculated using frequencies and
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41 157 percentages, means and SDs, medians and IQRs as appropriate. The outcome of interest was
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43 158 antibiotic prescription (yes/no), defined as an oral antibiotic prescription issued for an aRTC
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45 159 during an in-person consultation, irrespective of the number of antibiotics given. It included
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47 160 both regular and delayed prescriptions, the latter to be dispensed if symptoms persisted,
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49 161 typically after 48 to 72 hours. It did not include 'delayed instruction', i.e. directions to follow-
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51 162 up for a prescription if symptoms persisted or worsened.
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55 163 To control for clustering at the GP level, potential predictors of antibiotic prescription were
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57 164 assessed using population averaged models using generalised estimating equations (GEE).
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3 165 Frequency distributions of individual explanatory variables of interest were calculated and
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5 166 univariable associations between each variable and antibiotic prescription were subsequently
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7 167 assessed using unadjusted ORs and 95% CIs. Since we could not assume linearity to the
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9 168 outcome, all continuous variables were categorised. Individual signs and symptoms variables
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11 169 were only investigated if at least 5% of aRTC cases presented with that particular symptom.
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13 170 Multivariate Wald-type tests were performed on multi-level categorical variables to test the
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15 171 hypothesis of the overall association.
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17 172 Potential predictors were included in the multivariable model if significant at $p < 0.2$ at
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19 173 univariable level and excluded if there were issues with collinearity. A predictor was only
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21 174 kept in the multivariable model if it improved the model and its p -value was less than 0.05.
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23 175 Ultimately 4425 aRTC cases were included in the final multivariable model.
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29 176 **RESULTS**

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32 177 In this cohort of aRTC patients, 2034 (45.0%) received an antibiotic prescription, of which
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34 178 333 (16.4%) were delayed.
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37 179 **GP characteristics**

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39 180 Most GPs were male ($n=24$; 73%). Mean age (years) was 49 ± 12 and mean years of GP
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41 181 practice was 23 ± 11 . Eleven (33%) GPs worked exclusively in the public sector whilst 20
42
43 182 (61%) worked in the private sector (including private pharmacy clinics). Two (6%) worked in
44
45 183 both sectors. Table S1 summarises the GP characteristics.
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48

49 184 **Patient characteristics**

50
51 185 Just over half of patients were female ($n=2395$; 53.1%) and the median age was 29 years
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53 186 (IQR=12-48). Over a third had completed up to secondary school education ($n=3050$; 68.0%).
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55 187 Smoking was reported in 735 (16.5%) cases. A summary of the patients' sociodemographic
56
57 188 and lifestyle characteristics is presented in Table S2.
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60 189 **Factors associated with antibiotic prescribing**

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3 190 The univariable and multivariable associations between GP-, practice- and consultation-level
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5 191 factors (Table 1), patient sociodemographic factors (Table 2), clinical factors (Table 3), and
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7 192 antibiotic prescription are described below.

9
10 193 Univariable analysis revealed numerous factors associated with antibiotic prescribing. At GP-
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12 194 level, GP age was identified as an important predictor with GPs aged 60 and older being most
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14 195 likely to prescribe antibiotics. At consultation-level, regular clients and patients who asked for
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16 196 antibiotics were more likely to receive an antibiotic prescription. Patient sociodemographic
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18 197 factors associated with antibiotic prescription included female sex, patient age (particularly
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20 198 those aged 65 and older) and being a smoker. Finally, a number of patient health status factors
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22 199 were significantly associated with antibiotic prescription at univariable level, with the most
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24 200 important being fever $>38.5^{\circ}\text{C}$, tender cervical nodes and total number of signs and/or
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26 201 symptoms with the odds of prescription increasing as the number increased.

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30 202 In the final multivariable model, female GPs were 2.3 times more likely to prescribe
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32 203 antibiotics (95% CI 1.22-4.26) and, compared to younger GPs aged between 28 and 39 years,
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34 204 GPs aged 50 to 59 (OR=2.1, 95% CI 1.19-3.77) or 60 years and older (OR=34.7, 95% CI
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36 205 14.14-84.98) were more likely to prescribe antibiotics. Increasing patient age also increased
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38 206 the likelihood of receiving an antibiotic prescription, with patients aged 65 and older being the
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40 207 most likely to receive a prescription (OR=2.3, 95% CI 1.71-3.18). The more signs and/or
41
42 208 symptoms a patient presented with, the more likely they were to be given an antibiotic, with
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44 209 patients having four or more signs and/or symptoms being the most likely (OR=9.6, 95% CI
45
46 210 5.78-15.99). Additionally, patients with fever $>38.5^{\circ}\text{C}$ (OR=2.6, 95% CI 2.08-3.26),
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48 211 productive cough (OR=1.3, 95% CI 1.03-1.61), otalgia (OR=1.3, 95% CI 1.01-1.76), tender
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50 212 cervical nodes (OR=2.2, 95% CI 1.57-3.05), regular clients (OR=1.3, 95% CI 1.05-1.66),
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52 213 patients who requested antibiotics (OR=4.8, 95% CI 2.52-8.99) and smokers (OR=1.4, 95%
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54 214 CI 1.13-1.71), were also more likely to be prescribed an antibiotic. Conversely, patients with
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3 215 non-productive cough (OR=0.3, 95% CI 0.26-0.41), sore throat (OR=0.6, 95% CI 0.53-0.78),
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5 216 rhinorrhoea (OR=0.3, 95% CI 0.23-0.36) or dyspnoea (OR=0.6, 95% CI 0.41-0.83), were less
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7 217 likely to be given an antibiotic prescription.
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10 218 **DISCUSSION**

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14 219 This is the first study in Malta that identifies factors associated with antibiotic prescribing for
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16 220 aRTCs in the community, using surveillance data. While univariable analysis revealed
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18 221 numerous factors associated with antibiotic treatment, multivariable analysis identified
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20 222 several independent predictors of antibiotic prescription at different levels – provider, patient,
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22 223 consultation and clinical.
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26 224 Our results pertaining to GP factors both converge and diverge from prior research. It has
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28 225 been suggested that high consultation rates may result in higher antibiotic prescription and in
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30 226 fact a Norwegian study was able to confirm this association.²¹ In our study however, despite
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32 227 GPs experiencing rather high daily patient loads, this did not influence their antibiotic
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34 228 prescription.
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38 229 Similar to Akkerman et al.,²² more years of GP experience was associated with increased
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40 230 antibiotic treatment. In contrast, an Italian study concluded the opposite, although the
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42 231 antibiotic prescribing of both GPs and paediatricians in children was investigated.²³ Although
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44 232 we did not investigate years of GP practice specifically due to collinearity issues, we found a
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46 233 positive association between GP age and antibiotic prescription, which reflects the GPs' years
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48 234 of practice. In Malta, family medicine was recognised as a specialty in 2004, after which
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50 235 doctors were legally required to undergo specialist training in family medicine. Through the
51
52 236 'grandfather clause', doctors who started training in Malta before November 2003 were
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54 237 eligible to acquire specialisation under certain criteria, essentially exempting them from
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56 238 specialist training.²⁴ Lower antibiotic prescribing among younger GPs could be explained by
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3 239 the fact that they have more recently undergone specialist training. Older GPs may engage in
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5 240 more habitual behaviour and be in greater need of refresher courses and information on the
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7
8 241 latest antibiotic prescription guidelines.
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10 242 Although it is well established that male and female physicians engage in different interaction
11
12 243 and communication styles with patients,²⁵ few studies have investigated the association
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14 244 between GP sex and antibiotic prescribing. Two recent studies investigating antibiotic
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16 245 prescription for aRTCs specifically, found that female GPs prescribe fewer antibiotics²⁶
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18 246 particularly to female patients,²⁷ although the results were not statistically significant.
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20 247 Conversely, our findings revealed that female GPs in Malta are more likely to prescribe
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22 248 antibiotics. Although our sample is representative of the population for sex, we believe that
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24 249 further research is needed to explore and better explain this association.
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29 250 In our study, antibiotic treatment increased significantly with age, with the elderly (≥ 65 years)
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31 251 most likely to receive a prescription. The age-range of patients included in similar studies
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33 252 varies widely, with most only looking at patient subsets, making it difficult to compare
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35 253 findings on age. While we share similar results as studies carried out in Holland and
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37 254 Australia,^{28,29} in England/Wales and Sweden, high rates of antibiotic treatment were found
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39 255 among the elderly and children alike.^{30,31} In contrast, in Norway it was found that patients
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41 256 aged 80 and over actually had the lowest odds of receiving an antibiotic prescription, followed
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43 257 by children younger than 6 years.²¹ Given that young children are more likely to visit their
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45 258 paediatrician in Malta, it is possible that more severe cases were missed in this study and that
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48
49 259 the youngest age groups are underrepresented. The higher prescription rates among the elderly
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51 260 in Malta could suggest an augmented concern for their vulnerability towards severe
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53 261 infections, and an understanding that aRTCs in children are likely viral in origin.
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57 262 Similar to other studies,³²⁻³⁴ being a current smoker was identified as an independent
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59 263 predictor of antibiotic prescribing. Doctors may feel that smokers will deteriorate without
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3 264 antibiotics, however there is no evidence that antibiotics provide smokers greater clinical
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5 265 benefit or faster recovery.³³ Fever, productive cough, otalgia or tender cervical nodes were
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7 266 also found to be independent predictors of antibiotic prescribing. Conversely, presenting with
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10 267 a sore throat, non-productive cough, rhinorrhoea or dyspnoea led to a decreased likelihood of
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12 268 prescription. Fever is frequently reported as a significant predictor of antibiotic
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14 269 prescription.³⁴⁻³⁶ An Italian study investigating antibiotic prescription in young children,
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17 270 similarly found that otalgia, cervical adenopathy or absence of rhinorrhoea among others were
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19 271 associated with antibiotic prescription.³⁶ GPs could believe that certain clinical findings, that
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21 272 are often positively associated to prescription, indicate a bacterial infection or are a precursor
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23
24 273 for more serious illness.

25
26 274 Differentiating between bacterial and viral aetiologies based on signs and/or symptoms alone
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28 275 is challenging and a likely driver of antibiotic over-prescription. Although some symptoms
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30 276 suggest a possible bacterial infection and could warrant further investigation, most
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33 277 uncomplicated viral respiratory tract infections last between 5 and 7 days and peak in severity
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35 278 at days 3 to 6.³⁷ Given that most patients in this study presented within three symptomatic
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38 279 days, some may have benefitted from a wait and see approach or delayed prescription,
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40 280 without negative consequences. In fact, a study which examined antibiotic prescribing for
41
42 281 acute cough and its impact on recovery across 13 European countries found similar recovery
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44 282 rates in patients prescribed and not prescribed antibiotics.³⁸ The potential role individual
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46
47 283 symptoms play in inappropriate antibiotic use should not be overlooked, as an EU-study
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49 284 indicated that Maltese respondents take antibiotics primarily to treat symptoms as opposed to
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51 285 illnesses.¹⁷

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54 286 Being a regular client also contributed to increased likelihood of antibiotic prescribing in this
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56 287 study. Given the structure of primary healthcare in Malta, private sector GPs, who
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59 288 simultaneously compete for business and whose patients pay out-of-pocket, may be eager to
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3 289 please. In fact, research suggests that a trade-off may exist between prudent antibiotic use and
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5 290 cultivating a positive doctor-patient relationship.³⁹ This is also impacted by expectations and
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7 291 studies have shown that both doctors' belief that a patient expects antibiotics, and patients'
8
9 292 actual expectations for antibiotics are associated with antibiotic prescription.⁴⁰⁻⁴² Requesting
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11 293 antibiotics was an important predictor of antibiotic prescription in our study. Whilst some
12
13 294 studies have shown that providing an antibiotic prescription to such patients increased patient
14
15 295 satisfaction,^{39,40} others suggest that it does not, indicating instead that receiving information
16
17 296 when an antibiotic is expected but not needed is as important as receiving a prescription.⁴³
18
19 297 Whilst it is imperative to understand why patients expect antibiotics and what determines
20
21 298 patient satisfaction in Malta, GPs need to find alternative strategies to ensure patient
22
23 299 satisfaction without providing an unwarranted antibiotic prescription. One strategy is
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25 300 enhancing doctor-patient communication through communication skills training. Effective
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27 301 communication together with information tools could facilitate decision-making and empower
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29 302 doctors to decline antibiotic requests when unnecessary.⁴⁴ This is important, as receiving an
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31 303 antibiotic, particularly when expected, reinforces patients' desire for prescriptions and their
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33 304 perception that they should consult a GP for a similar problem in the future.⁴⁵
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40 305 A study carried out in Spain also showed that having access to point-of-care tests (rapid
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42 306 antigen detection tests and C-reactive protein) was associated with an 18.9% lower antibiotic
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44 307 prescription rate among antibiotic-requesting patients.⁴⁶ Having access to rapid tests could
45
46 308 help GPs support their decision not to prescribe by reducing uncertainty thereby lessening the
47
48 309 risk that they give in to patient demand, whilst providing reassurance to patients.^{46,47} In Malta,
49
50 310 point-of-care tests are largely unavailable, which may augment diagnostic uncertainty.
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52 311 Coupled with patient demand for antibiotics, this exerts prescribing pressure on GPs and may
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54 312 result in an unnecessary prescription. Malta possesses a culture that scores high for
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56 313 uncertainty avoidance, a cultural dimension that has consistently been reported as a potent
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3 314 driver for unnecessary antibiotic use.^{14,15,48} Efforts should be made to make low-cost, rapid
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5 315 diagnostics more readily available since these could reduce diagnostic uncertainty and lessen
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7 316 the pressure to prescribe an empiric antibiotic. However, their introduction must be
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10 317 approached with caution to avoid introducing new elements of uncertainty, addressing system
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12 318 factors such as the out-of-pocket cost of tests on the overall consultation, combined with
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14 319 training and support to encourage acceptance. Likewise, patients should be informed about
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16
17 320 the possibility of low-cost testing to avoid unnecessary antibiotic consumption, thereby
18
19 321 safeguarding themselves and their future.

21 322 **Strengths and limitations**

23
24 323 Knowledge on the drivers of antibiotic prescribing in southern European countries with high
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26 324 antibiotic consumption rates is largely lacking, limiting our ability to develop targeted
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28 325 interventions. A first of its kind in Malta, this study paves the way for more research on
29
30 326 antibiotic prescribing for aRTCs and other indications in the outpatient sector. The sample of
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32
33 327 4518 aRTC cases was sufficient to analyse a large number of potential explanatory variables
34
35 328 in multivariable analysis. Data collection tools were adapted from materials used in previous
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37 329 research^{49,50} and piloted in the Maltese context. Through user-friendly surveillance forms, we
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39
40 330 acquired data on provider, patient, consultation and clinical factors which could impact
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42 331 antibiotic prescribing, allowing for deeper analysis of potential influencing factors compared
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44 332 to studies that only examine a subset of these characteristics. The simple to complete forms
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46
47 333 were intended to aid documentation of as many aRTC cases as possible, while reducing GP
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49 334 dropouts and non-reporting. Given its design and incorporation into clinical practice, it may
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51 335 have helped reduce the effect of observation bias.¹⁰

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54 336 Still, this study does have limitations. Since GPs participated voluntarily, it is possible that
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56 337 participants were more interested in the research area or more conservative prescribers than
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58 338 non-participating GPs. Therefore our GP sample may not be representative of all Maltese
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3 339 GPs. The audit-based nature of the study may have resulted in measurement error; it is
4
5 340 possible that GPs completed patient background information that was atypical to ask during a
6
7 341 normal consultation without directly asking the patient. It is also possible that variables of
8
9 342 interest located at the end of the surveillance sheet were left unmarked and inaccurately
10
11 343 assumed to be non-cases. Lastly, GPs were issued three-monthly feedback reports and since
12
13 344 audit and feedback is a behaviour change intervention in itself it is possible that the antibiotic
14
15 345 prescribing rate has been affected as a result of it. However, prior research on the association
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17 346 between surveillance participation and GPs' antibiotic prescription patterns has produced
18
19 347 mixed results; a recent randomised control trial reported no effect.⁵¹
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24 348 **CONCLUSION AND IMPLICATIONS FOR RESEARCH AND POLICY**

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28 349 Our study sheds light on key drivers of community-level antibiotic prescribing for aRTCs in
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30 350 Malta, providing missing scientific evidence necessary to develop tailored interventions
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32 351 aimed at improving prudent antibiotic use. Furthermore, we believe that our study could help
33
34 352 guide antimicrobial stewardship initiatives in the community in countries with similar
35
36 353 sociocultural traits.

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39 354 Addressing inappropriate antibiotic prescribing in primary care requires multifaceted
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41 355 interventions that focus on educating providers and patients alike, whilst providing them with
42
43 356 the tools required to ensure that antibiotics are prescribed appropriately and taken only when
44
45 357 necessary. Although more experienced GPs could benefit from targeted antibiotic stewardship
46
47 358 activities, ongoing continuing medical education initiatives for all GPs are important to ensure
48
49 359 that appropriate antibiotic prescription practices are maintained. Communication training in
50
51 360 particular is needed to facilitate decision-making and empower doctors to decline antibiotic
52
53 361 requests. National antibiotic guidelines should include other diagnostic criteria such as
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55 362 smoking status and better promote the use of delayed antibiotic prescription, particularly in
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57 363 high-prescription contexts. Finally, in settings with high uncertainty avoidance, improving
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364 access to low-cost, rapid tests could prove beneficial in supporting GPs' prescribing
365 decisions.

For peer review only

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375 **AUTHORS' CONTRIBUTIONS**

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

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3 391 None declared.
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6 392 **ETHICAL APPROVAL**
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9 393 The University of Malta Research Ethics Committee granted ethical approval and research
10
11 394 was conducted in accordance with the Declaration of Helsinki. GP participation was voluntary
12
13 395 and informed consent was obtained. GPs could terminate participation at any time, for any
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15 396 reason, without consequence. GP identities were masked using randomly assigned unique
16
17 397 identification codes and no personal information was made public. Finally, all patient data
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19 398 collected by GPs was non-identifiable.
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23 399 **DATA AVAILABILITY STATEMENT**
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26 400 All data relevant to the study are included in the article or uploaded as supplementary
27
28 401 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)	
	<10	183	(23.7)	589	(76.3)	1	0.026#		
Years of practice as a GP (n=4,502)	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)			
	<22	1,090	(49.0)	1,135	(51.0)	1	0.488	–	–
Total no. of patients examined per day (n=4,436)	≥22	913	(41.3)	1,298	(58.7)	0.95 (0.83-1.09)		–	–
	full-time	1,437	(42.2)	1,966	(57.8)	1	0.217	–	–
Type of employment	part-time	597	(53.5)	518	(46.5)	1.45 (0.80-2.60)			
	group	643	(39.5)	987	(60.5)	1	0.062	–	–
Type of practice[†]	solo	1,391	(48.2)	1,497	(51.8)	1.73 (0.97-3.08)			
	public healthcentre clinic	318	(34.2)	611	(65.8)	1	0.063#		
Location of GP practice	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)			
	clinic	1,428	(44.8)	1,759	(55.2)	1	0.016	–	–
Location of consultation (n=4,263)	home	466	(43.3)	610	(56.7)	1.20 (1.03-1.38)			
	no	991	(38.9)	1,558	(61.1)	1	0.021	1	0.016
Regular client	yes	1,043	(53.0)	926	(47.0)	1.23 (1.03-1.48)		1.32 (1.05-1.66)	
	no	1,983	(44.6)	2,459	(55.4)	1	0.000	1	0.000
Antibiotics requested	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

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 (>38.5°C), 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

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)			
	1	405	(37.1)	687	(62.9)	1	0.000 [#]	1	0.000
No. of signs and symptoms (n=4,497)	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)	
	no	1,070	(33.4)	2,138	(66.6)	1	0.000	1	0.000
Fever (>38.5°C)	yes	964	(73.6)	346	(26.4)	4.74 (4.12-5.45)		2.60 (2.08-3.26)	
	no	1,153	(36.8)	1,983	(63.2)	1	0.000	1	0.028
Productive cough	yes	881	(63.8)	501	(36.2)	2.49 (2.19-2.83)		1.29 (1.03-1.61)	
	no	1,701	(55.1)	1,384	(44.9)	1	0.000	1	0.000
Non-productive cough	yes	333	(23.2)	1,100	(76.8)	0.35 (0.31-0.41)		0.33 (0.26-0.41)	
	no	1,055	(44.8)	1,300	(55.2)	1	0.099	1	0.000
Sore throat	yes	979	(45.3)	1,184	(54.7)	1.10 (0.98-1.23)		0.64 (0.53-0.78)	
	no	1,530	(53.8)	1,312	(46.2)	1	0.000	1	0.000
Rhinorrhoea	yes	504	(30.1)	1,172	(69.9)	0.41 (0.36-0.47)		0.28 (0.23-0.36)	
	no	1,795	(43.7)	2,315	(56.3)	1	0.000	1	0.043
Otalgia	yes	239	(58.6)	169	(41.4)	1.62 (1.34-1.97)		1.33 (1.01-1.76)	
	no	1,777	(42.6)	2,397	(57.4)	1	0.000	1	0.000
Tender cervical nodes	yes	257	(74.7)	87	(25.3)	4.08 (3.22-5.16)		2.19 (1.57-3.05)	
	no	1,908	(44.8)	2,350	(55.2)	1	0.001	1	0.003
Dyspnoea	yes	126	(48.5)	134	(51.5)	1.51 (1.19-1.92)		0.58 (0.41-0.83)	
	no	1,860	(43.7)	2,397	(56.3)	1	0.000	–	–
Sibilant rhonchi	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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For peer review only

SUPPLEMENTARY FILES (1)

GP code [for office use only]:

GP demographics

Date: _____

1) Date of birth:		
2) Sex: <input type="checkbox"/> Male <input type="checkbox"/> 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 ?		<input type="checkbox"/> Yes <input type="checkbox"/> No
9c) Are you currently a trainee?		<input type="checkbox"/> Yes <input type="checkbox"/> No
10) Years of practice as a GP:		
11) How much do you currently work? <input type="checkbox"/> Part-time <input type="checkbox"/> 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
	<input type="checkbox"/> Public sector	<input type="checkbox"/> Healthcare centre <input type="checkbox"/> Home visits
	<input type="checkbox"/> Solo practice	<input type="checkbox"/> Private clinic <input type="checkbox"/> Pharmacy clinic <input type="checkbox"/> Home visits
	<input type="checkbox"/> Group practice	<input type="checkbox"/> Private clinic <input type="checkbox"/> Pharmacy clinic <input type="checkbox"/> Home visits
	<input type="checkbox"/> 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)
	<input type="checkbox"/>
	<input type="checkbox"/>
	<input type="checkbox"/>
	<input type="checkbox"/>
	<input type="checkbox"/>
	<input type="checkbox"/>
	<input type="checkbox"/>

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)
	<10	6	(18.7)
Years of GP practice (n=32)	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

3 SUPPLEMENTARY FILES (3)

4
 7 **Table S2. Sociodemographic and lifestyle characteristics of patients with**
 8 **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)
Educational level (n=4,484)	≥65	497	(11.0)
	pre-school	496	(11.1)
	primary	751	(16.7)
	secondary	1,803	(40.2)
	upper-secondary	776	(17.3)
	tertiary	545	(12.2)
Household size (persons/household) (n=4,465)	none achieved	113	(2.5)
	1-2	1,087	(24.3)
	3-4	2,687	(60.2)
Contact with children <5 years (n=4,481)	≥5	691	(15.5)
	no	2,881	(64.3)
Current smoker (n=4,453)	yes	1,600	(35.7)
	no	3,718	(83.5)
	yes	735	(16.5)

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

		(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.