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Investigating the Mechanism of Impact of the Quality Premium Initiative on Antibiotic Prescribing in Primary Care Practices in England: A Study Protocol.

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Title: Investigating the Mechanism of Impact of the Quality Premium Initiative on Antibiotic Prescribing in Primary Care Practices in England: A Study Protocol.

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33 **Abstract**

34 **Introduction**

35 The persistent development and spread of resistance to antibiotics remains an important public
36 health concern in the UK and globally. About 74% of the antibiotics prescribed in England in
37 2016 was in primary care. The Quality Premium (QP) initiative that rewards Clinical
38 Commissioning Groups financially based on the quality of specific health services
39 commissioned is one of the NHS England interventions to reduce antimicrobial resistance
40 through reduced prescribing. Emerging evidence suggests a reduction in antibiotic prescribing
41 in primary care practices in the UK following QP initiative. This study aims to investigate the
42 mechanism of impact of this high-cost health-system level intervention on antibiotic
43 prescribing in primary care practices in England.

44 **Methods and analysis**

45 The study will constitute secondary analyses of antibiotic prescribing data for almost all
46 primary care practices in England from the NHS England Antibiotic Quality Premium
47 Monitoring Dashboard and OpenPrescribing covering the period 2013 to 2018. The primary
48 outcome is the number of antibiotic items per Specific Therapeutic group Age-sex Related
49 Prescribing Unit (STAR-PU) prescribed monthly in each practice or CCG. We will first
50 conduct an interrupted time series using the Ordinary Least Square regression method to
51 examine whether antibiotic prescribing rate in England has changed over time, and how such
52 changes, if any, are associated with the QP implementation. Single and sequential multiple-
53 mediator models using a unified approach for the natural direct and indirect effects will be
54 conducted to investigate the relationship between the QP initiative, the potential mediators and
55 antibiotic prescribing rate with adjustment for the practice and CCG characteristics.

56 **Ethics and dissemination**

57 This study will use secondary data that are anonymised and obtained from studies that have
58 either undergone ethical review or generated data from routine collection systems. Multiple
59 channels will be used in disseminating the findings from this study to academic and non-
60 academic audiences.

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3 **63 Strengths and Limitations of this study**
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6 64 • This study will be the first to evaluate the mechanism of the impact of a financial
7 65 incentive initiative involving Clinical Commissioning Groups to improve antibiotic
8 66 prescribing in primary care practices in England.
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11 67 • The investigation of multiple mediators in this study will help to identify the
12 68 contributions of multiple strategies in translating the effects of QP while unpacking the
13 69 extent of the effect of specific mediators.
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16 70 • Due to the limited data on practice-level interventions or strategies that might
17 71 potentially mediate the effect of the QP on antibiotic prescribing, we will not be able to
18 72 extensively investigate the mechanism of QP impact at the practice level.
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21 73 • Nevertheless, extensive investigations will be conducted at CCG level where the
22 74 Quality Premium initiative is implemented, and rewards paid out.
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76 Introduction

77 The persistent development and spread of resistance to antimicrobials, especially antibiotics,
78 remains an important public health concern in the UK¹ and globally.^{2,3} Antimicrobial resistance
79 (AMR) is a major threat to the treatment and control of infectious diseases as drug-resistant
80 infections are characterised by prolonged morbidity, increased risk of disabilities, death, and
81 cost of healthcare.⁴ A 2014 review estimated that consistent increases in AMR would lead to
82 about 10 million deaths per year by 2050.⁵ Inappropriate prescribing and use of antibiotics in
83 healthcare practices, especially primary care, are integral to the development and spread of
84 resistance.^{6,7}

85 About seventy-four per cent of the antibiotics prescribed in England in 2016 was in primary
86 care.⁸ The high rate of antibiotic prescribing in primary care has been associated with increased
87 antimicrobial resistance.⁹ While some of the antibiotics prescribed in primary care settings are
88 appropriate, a substantial proportion are cases where antibiotics are not clinically indicated,
89 such as suspected respiratory tract conditions which can be self-limiting.^{9,10} Uncertainties about
90 diagnosis, (perceived) patient expectations for antibiotics, occupational pressure (e.g.
91 consultation rate) and previous experiences, are some of the identified drivers of
92 overprescribing in primary care practices.¹¹⁻¹⁶

93 Interventions such as antibiotic stewardship programmes, education and training initiatives
94 targeted at prescribers and patients, financial incentives, among others have been implemented
95 in England to reduce antimicrobial resistance through reduced prescribing. In particular, the
96 Quality Premium (QP) is an NHS England initiative established in 2013 to reward Clinical
97 Commissioning Groups (CCGs) financially based on the quality of specific health services
98 considered to be of national or local priority and commissioned over a specific period.¹⁷
99 Improvement of antibiotic prescribing in primary care was one of the national priorities in the
100 2015/16 guidance,¹⁸ constituting 10% of the premium awarded from 2016/17 to date.^{19,20} Key
101 aspects of the 'improved antibiotic prescribing' priority are reductions in the number of
102 antibiotics prescribed in primary care facilities across England, and in the proportion of broad-
103 spectrum antibiotics prescribed in primary care (2015-2017).¹⁹ Part of the requirements in the
104 2015/16 QP guidance for demonstrating improved antibiotic prescribing by CCGs was a
105 reduction in the number of antibiotics prescribed in primary care by 1% of the mean value in
106 England in 2013/14 (i.e. 1.61 items per Specific Therapeutic group Age-sex Related
107 Prescribing Unit (STAR-PU)). This was further increased to 4% in the 2016/17 guidance.

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3 108 Emerging evidence suggests a reduction in antibiotic prescribing in primary care practices in
4
5 109 the UK following the QP initiative.^{21,22} Prescribing data from England shows a reduction of
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7 110 about 2.7 million antibiotic items between 2014/15 and 2016/17 financial year.²³ Eighty-eight
8
9 111 per cent of the CCGs in England achieved the target of reducing antibiotic prescribing in the
10
11 112 first two years of QP.²¹ Also, there has been a significant reduction in the proportion of broad-
12
13 113 spectrum antibiotics prescription with 83% of the CCGs meeting their target in the first two
14
15 114 years.²¹ Such reductions in antibiotic prescribing would be expected to contribute to reductions
16
17 115 in the development of resistance.²⁴ However, little is known about the mechanisms by which
18
19 116 the QP initiative impacted on antibiotic prescribing in primary care practices.

20 117 The impact of interventions on specific outcomes are sometimes explained by a series of
21
22 118 events. Potential mediators are important in assessing causal relationships like that between QP
23
24 119 and antibiotic prescribing in primary care practices in England; where a *potential mediator* is
25
26 120 a variable that hypothetically mediates the effect of QP on the outcome. The conceptual model
27
28 121 shown in fig.1 demonstrates the hypothesised pathways for the impact of the QP initiative on
29
30 122 antibiotic prescribing, and subsequently AMR. The model is developed based on conceptual
31
32 123 and empirical evidence from existing literature and the results of qualitative and survey studies
33
34 124 conducted as initial stages of the broader STEP-UP (Improving the uptake and Sustainability
35
36 125 of Effective interventions to promote Prudent antibiotic Use in Primary care)²⁵ project that
37
38 126 includes the current study. The conceptual model will be further validated through a
39
40 127 stakeholder workshop with key antibiotic stewardship personnel, primary care prescribers, and
41
42 128 CCG representatives.

43 129 Our conceptual model suggests that in addition to its direct impact, the QP initiative acts by
44
45 130 stimulating and enhancing the adoption of existing strategies to reduce and optimise antibiotic
46
47 131 prescribing. In investigating the potential pathways connecting QP to reductions in antibiotic
48
49 132 prescribing, we will be examining the hypothesis that factors like the Chief Medical Officer's
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51 133 (CMO) letter, TARGET toolkit, antibiotic auditing, benchmarking, local incentives at CCG
52
53 134 level, prescribers and patients' antimicrobial stewardship (AMS) education/training can
54
55 135 transmit part of the influence of the QP initiative to antibiotic prescribing.

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57 136 **[insert fig. 1]**

58
59 137 First implemented in September 2014, the CMO letter, which provided social norm feedback
60
138 to primary care practitioners in England whose antibiotic prescribing rate was in the top 20%,

1
2
3 139 reduced antibiotic prescribing by 3.3% in six months in a randomised trial.²⁶ The criteria for
4 140 selecting practices that received the letters in the subsequent years changed with the addition
5 141 of measures like a change in antibiotic prescribing over time, and whether practices have
6 142 previously been sent CMO letter.

7
8 143 Another important mediator hypothesised in our conceptual model is AMS education/training
9 144 of prescribers and patients. Educating and training prescribers on the importance of antibiotic
10 145 stewardship and ways to promote prudence can help prescribers make better decisions on when
11 146 an antibiotic is indicated and can also improve patients' knowledge on the appropriate use of
12 147 antibiotics. AMS interventions targeted at patients can improve their knowledge of when
13 148 antibiotics are not needed, increase confidence and skills on how to self-care, which can result
14 149 in reduced consultations for self-limiting illness and thus reduced antibiotic prescriptions.

15
16
17 150 Treat Antibiotics Responsibly, Guidance, Education, Tools (TARGET) is a toolkit developed
18 151 by the Public Health England, the Royal College of General Practitioners and other
19 152 professional societies to promote prudent antibiotic use among prescribers and patients in
20 153 primary care.²⁷ The intervention comprises of multiple resources (patient information leaflets
21 154 on infection management and antibiotic use, self-assessment checklist for prescribers,
22 155 antibiotic audit toolkits, interactive workshop presentations, national antibiotic management
23 156 guidance, training resources, and resources for clinical and waiting areas) to provide clinicians
24 157 and patients with the motivation and skills to use antibiotics prudently.²⁷ A qualitative study
25 158 evaluating prescribers' attitude and perception about the TARGET toolkit reported that general
26 159 practitioners described it as useful and important in improving their prescribing behaviours and
27 160 the expectations of their patients.²⁸ The use of resources like the TARGET antibiotics
28 161 workshop have been shown to reduce antibiotic prescribing rate in a randomised controlled
29 162 trial.²⁹

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31
32 163 We hypothesise that the implementation of the QP initiative informed the initiation or wider
33 164 use of these strategies indicated in the conceptual model as mediators, which will subsequently
34 165 influence antibiotic prescribing at primary care practices.

35
36
37 166 The implementation of the QP initiative in NHS England constitutes a natural experiment and
38 167 offers an opportunity to investigate the pre and post-intervention periods to understand the
39 168 mechanism of impact of the QP intervention in reducing antibiotic prescribing rates across the
40 169 whole of primary care.³⁰ Given the ethical and practical constraints in manipulating exposure
41 170 in such an intervention, a natural experimental design offers a practical approach to understand

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3 171 the overall effect and mechanism of interventions like QP that offer financial incentives for
4
5 172 clinical compliance. The publication of the 2015/16 QP Guidance¹⁸ constitutes the
6
7 173 'intervention', with periods before this as the 'control'.
8

9 174 **Study Aim and Objectives**

10
11 175 Using routinely collected population-level datasets on antibiotic prescribing in England, this
12
13 176 study aims to address the research question: What are the mechanisms and mediators of the
14
15 177 impact of a high-cost health-system level intervention, the 'antibiotic prescribing quality
16
17 178 premium'? We will investigate the difference in antibiotic prescribing rate pre and post-QP
18
19 179 initiative to establish its direct, indirect (through mediators), and total effects in reducing
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21 180 antibiotic prescribing in primary care practices in England.

22 181 **Methods and Analysis**

23 182 **Study Design**

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27 183 Contemporary evaluations of the effectiveness of health policies go beyond estimating their
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29 184 total effect on outcomes. Mediation analysis decomposes the total effect of an intervention into
30
31 185 separate causal pathways,³¹ enabling an understanding of why and how policies work by
32
33 186 estimating the direct and indirect effects of the exposure.³² We will conduct mediation analyses
34
35 187 investigating the potential mediators of the impact of QP on antibiotic prescribing in primary
36
37 188 care in England, establishing the direct and indirect effects of the QP initiative.

38 189 **Data sources**

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40
41 190 The study will constitute secondary analyses of antibiotic prescribing data from NHS England
42
43 191 covering the period 2013 to 2018. CCGs were established in England in April 2013 following
44
45 192 the Health and Social Care Act 2012.³³ Data on antibiotic prescribing in primary care at CCG
46
47 193 levels will be sourced from the NHS England Antibiotic Quality Premium Monitoring
48
49 194 Dashboard, which is produced by the NHS Business Services Authority (BSA).³⁴ Primary Care
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51 195 prescribing data is publicly available from the NHS BSA website. The dataset contains the
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53 196 number of antibiotic items (STAR-PU) prescribed in each CCG from the financial year 2015/16
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55 197 to 2018/19, with data for October 2018 the latest at the time of this protocol. Data for the period
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57 198 2013 to 2015 will be mapped to CCG-level from the practice-level data.

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59 199 Practice-level antibiotic prescribing data will be sourced from OpenPrescribing, an Evidence-
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200 Based Medicine DataLab project by the University of Oxford. OpenPrescribing publishes

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3 201 monthly antibiotics prescribing data from August 2013, with data for October 2018 the latest
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5 202 at the time of this protocol. Practice-level antibiotic prescribing data from OpenPrescribing is
6
7 203 not STAR-PU weighted, so the extracted data will be STAR-PU weighted using figures from
8
9 204 the 2013 Item-based age–sex weighting for oral antibacterials,¹⁴ and the number of registered
10
11 205 patients in each age-gender category in a practice for each specific month.

12
13 206 Overall, the dataset offers coverage of at least three years post-intervention given that antibiotic
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15 207 prescribing became a QP priority in March 2015. This will be important in investigating the
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17 208 immediate direct and indirect effects of the QP initiative while giving an insight into the
18
19 209 sustainability of the identified effects (if any) in the long-term.

20 210 **Variables**

21
22 211 The predictor will be a binary variable indicating the implementation of the QP intervention.
23
24 212 The intervention will include all periods after March 2015 when the 2015/16 QP guidance in
25
26 213 England was published, while the control will be periods prior to this. The primary outcome of
27
28 214 interest is the rates of antibiotic prescribing at CCG level in England, which will be a
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30 215 continuous variable indicating the number of items (per STAR-PU) prescribed per month.

31
32 216 To account for differences in practice and CCG characteristics that can contribute to variance
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34 217 in antibiotic prescribing, we will be adjusting for the number of General Practitioners in each
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36 218 practice (from the NHS Workforce data),³⁵ the index of multiple deprivation (from the
37
38 219 Department for Communities and Local Government),³⁶ prevalence of co-morbidities -asthma,
39
40 220 chronic obstructive pulmonary disease (COPD), diabetes, cancer, chronic kidney disease (from
41
42 221 the NHS Quality and Outcomes Framework database),³⁷ and seasonal flu vaccination rate (from
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44 222 Public Health England).³⁸

45 223 Mediator variables will be derived from the questionnaire data from a PHE survey³⁹ with 187
46
47 224 of the 209 AMS leads representing CCGs in England and data from other organizations that
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49 225 have evaluated the interventions treated as potential mediators in this study. In the PHE survey,
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51 226 participants were required to complete questionnaire items which included their adoption of
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53 227 national and local strategies in their respective CCG to enable them to meet QP targets on
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55 228 antibiotic prescribing in primary care. The mediator variables will be binary or continuous
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57 229 variables indicating the adoption of key interventions and intermediaries that are hypothesised
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59 230 to reflect in the integration of the QP guidance in improving antibiotic prescribing in primary
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231 care practices.

232 **Handling missing data**

233 Over the period covered by this study (2013-2018), there have been changes in the number of
234 practices and CCGs in England. Some practices have closed, new practices opened, and some
235 CCGs merged over the period; as such we have missing values for some observations. To
236 maximize the use of existing observations, we will retain all observed values in the main
237 analysis and impute the missing values using multiple approaches.⁴⁰ Missing values for the
238 period before a new CCG was formed through merger of pre-existing CCGs will be imputed
239 using the mean value of the CCGs that constitutes the merger; subsequently, these closed CCGs
240 will be dropped from the dataset. Other missing values in this study will be handled using
241 multiple imputation method on Mplus V.8.2. We will run a separate imputation model for the
242 practice and CCG level datasets, the results will be averaged across 20 imputed datasets.
243 Complete case analysis will be conducted as part of the sensitivity analyses for this study to
244 examine the consistency of the results from the imputed set.

245 **Statistical analysis**

246 Our first analysis will be an interrupted time series to investigate whether antibiotic prescribing
247 rate in England has changed over time, and how such changes, if any, are associated with the
248 QP implementation in March 2015. This will be conducted using the Ordinary Least Square
249 regression method⁴¹ to assess whether the 2015/16 QP establishment resulted in a shift in the
250 level and trend in antibiotic prescribing in primary care in England, compared to the period
251 before the intervention. Using the practice-level dataset, a univariate time series with the mean
252 antibiotic items (STAR-PU weighted) prescribed in all primary care practices in England for
253 each month will be conducted using the *ITSA* function on Stata, with *posttrend* specification to
254 show a post-intervention trend. The Cumby-Huizinga general test for autocorrelation will be
255 used for general specification test of serial correlation in the time series data.⁴²

256 A new Quality Premium guideline was implemented each financial year with changes in the
257 prescribing rate target and the proportion that improved prescribing constituted in the QP award
258 for each year. Our mediation analyses will investigate the effects of the QP by comparing
259 antibiotic prescribing rate in the financial year before its implementation to each subsequent
260 year post-implementation; as such our dataset for the mediation analyses will have the control
261 group as the financial year before QP and the intervention group as a specific post-QP
262 implementation year. Three analyses will be conducted for each of the three financial years
263 since QP establishment. This will enable us to compare the effects of the different target levels

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3 264 that have been set over the years, and the proportions of the QP award attributed to
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5 265 improvement in antibiotic prescribing.
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7 266 Using a unified model for the natural direct and indirect effects,³¹ we will investigate the
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9 267 relationship between the QP initiative, the potential mediators and antibiotic prescribing rate
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11 268 with adjustment for the practice and CCG characteristics. This approach addresses the issues
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13 269 associated with the traditional approach to mediation analysis that obtains natural direct and
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15 270 indirect effect estimates through a nontrivial combination of parameter estimates from multiple
16
17 271 models for the regression of the mediator and that of the outcome.^{43,44} Also, the unified model
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19 272 is applicable to nonlinear regressions, different measurement types for outcome and mediator
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21 273 variables, and allows for interaction between the exposure and the mediator.³¹

22 274 We will first fit single-mediator models with each mediator separately modelled using the
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24 275 *medeff* function in Stata.⁴⁵ With the single-mediator models, we will be able to establish the
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26 276 individual influence of each potential mediator variable. Based on their effect size and
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28 277 significance of the mediating pathway in the single-mediator models, the mediators will be
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30 278 individually added to build a multiple-mediator model using a sequential mediation analysis
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32 279 method.⁴⁶

33 280 A sequential multiple mediators analysis is preferred to merely summing the effects of the
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35 281 single mediators because this sum may differ from the joint mediated effect; particularly as our
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37 282 potential mediators may influence one another.⁴⁶ Modelling all the significant mediators
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39 283 together provides a more accurate assessment of the mediation effects and causal
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41 284 relationship^{47,48} while assessing the indirect effect of a group of mediators in explaining how
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43 285 and why the intervention impacts on the outcome. The decision on the causal ordering of the
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45 286 mediators in the sequential mediation analysis will consider the effect size from the single-
46
47 287 mediator models and evidence from the literature. All analysis will be conducted in the STATA
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49 288 statistical package version 15.1.

289 **Sensitivity analyses**

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51 290 Sensitivity analyses using dummy implementation dates of one to three months before and after
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53 291 the actual month each of the QP guidance were published will be conducted to assess the
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55 292 difference between the time the guidance is published and the dissemination of information
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57 293 and development of local arrangements by the CCGs. These analyses will further help to
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59 294 investigate the anticipatory effect of the policy and whether lag in implementation attenuates
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295 the effect of the intervention.

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3 296 Also, we will conduct separate analysis with the outcome variable (antibiotic prescribing rate)
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5 297 as a binary variable (indicating whether each CCG achieved the required rate of reduction in
6
7 298 antibiotic prescribing as stated in the QP guidance for each year) to examine whether the
8
9 299 classification of the outcome variable based on achievement of QP target influences the results.

10
11 300 Subgroup analyses will be conducted on clusters of primary care practices based on their
12
13 301 antibiotic prescribing behaviour (high and low prescribers) and indices of deprivation to
14
15 302 examine whether any effect of the QP initiative seen in the overall population is different in
16
17 303 subgroups of practices. The top and bottom 20% antibiotic prescribers as of March 2015 will
18
19 304 be categorised as high and low prescribers. To address the issue of regression to mean in
20
21 305 subgroup analyses, we will build a separate model with categorization into high and low
22
23 306 prescribers based on the mean of the prescribing rate of practices in the last three months to
24
25 307 March 2015. The use of mean of multiple measures will offer a better estimate of each
26
27 308 practice's true mean before the 2015/16 Quality Premium initiative.⁴⁹ The subgroup analysis
28
29 309 based on the indices of deprivation data^{36,50} at primary-care practice level will be important in
30
31 310 establishing the equity impact of the QP initiative.

311 **Limitations**

312 This study has some limitations. The survey that provided data on mediator variables included
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314 187 of the 209 CCGs existing as at the time of the study. However, this sample size is large
315
316 enough for strong statistical power, and multiple imputation will be used to address issues on
317
318 missingness. Furthermore, due to the limited data on practice-level interventions or strategies
319
320 that might potentially mediate the effect of the QP on antibiotic prescribing, we will not be able
321
322 to extensively investigate the mechanism of QP impact at the practice level. Nevertheless,
323
324 extensive investigations will be conducted at CCG-level where we have more data on potential
325
326 mediators.

327
328 In 2013, the Primary Care Trusts (PCTs) in England, which were responsible for planning and
329
330 commissioning health care services at the primary care level, were transformed to Clinical
331
332 Commissioning Groups.⁵¹ As such, our investigations are restricted to the CCG era. This is
333
334 important as the Quality Premium initiative is implemented, and rewards paid out at CCG level.

335 **Discussion**

336 Although the Quality Premium intervention has been reported to have been effective in
337
338 reducing antibiotic prescribing,²² there remain important gaps in the evidence base for this
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1
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3 327 intervention, especially in relation to its mechanism of impact. This study will be the first to
4
5 328 evaluate the mechanism of the impact of a financial incentive initiative involving CCGs to
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7 329 improve antibiotic prescribing in primary care practices in England. If our study identifies some
8
9 330 key mediators, like other interventions implemented in similar time or in response to the QP
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11 331 initiative, that explain the indirect effect of the QP intervention on antibiotic prescribing, this
12
13 332 will provide important evidence on the effectiveness of the implementation of a package of
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15 333 interventions on antibiotic prescribing. The investigation of multiple mediators in this study
16
17 334 will also help to highlight the contributions of multiple factors in translating the effects of QP
18
19 335 while unpacking the extent of the effect of specific mediators.

20
21 336 Evidence on the mechanism of impact of strategies like QP will be important in improving its
22
23 337 uptake and sustainability while maximizing its potential in reducing antibiotic prescribing in
24
25 338 primary care settings.

26
27 339 Finally, financially-incentivized strategies for clinical compliance have been criticised for their
28
29 340 ability to result in unintended consequences.⁵² In the case of the QP initiative, unintended
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31 341 consequences like not prescribing antibiotics in cases where they are indicated are possible.
32
33 342 However, some of the QP response strategies that we hypothesised as potential mediators (such
34
35 343 as prescribers' AMS education/training) have the ability to mitigate this unintended
36
37 344 consequence. By comparing the prescribing rate before and after the QP initiative and
38
39 345 identifying the strategies that explain its effect, we will generate evidence that will be important
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41 346 in considerations of the future of this intervention and revisions that may help reduce potential
42
43 347 unintended consequences.

44 348 **Patient and public involvement**

45
46 349 This study will use secondary data mostly from routine collection system and will not directly
47
48 350 involve patients. The engagement workshop with stakeholders will involve primary care
49
50 351 practitioners and CCG representatives.

51 352 **Ethics and dissemination**

52
53 353 This study will use secondary data that are anonymised and obtained from studies that have
54
55 354 either undergone ethical review or generated data from routine collection systems. Prescribing
56
57 355 data from NHS BSA and NHS Digital are generated from routinely collected prescribing data
58
59 356 on items that have been dispensed in primary care practices in England. The survey that
60
357 produced the data on mediator variables was registered with the Public Health England

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2
3 358 Research Support and Governance Office (RSGO) and approved by Public Health England
4
5 359 Research Ethics and Governance Group (REGG) and Health Research Association (HRA).
6

7 360 Multiple channels will be used in disseminating the findings from this study to academic and
8
9 361 non-academic audiences. With will include an engagement workshop with our stakeholder
10
11 362 network, presentations in scientific conferences, publication in peer-reviewed journals, press
12
13 363 conference coinciding with paper publications.
14

15 364 **Patient and public involvement**

16
17 365 This study will not involve patients. The study will constitute secondary analyses of routinely
18
19 366 collected data. The dissemination of the results will include communication channels and
20
21 367 public engagement events that will involve prescribers and AMS leads.
22

23 368

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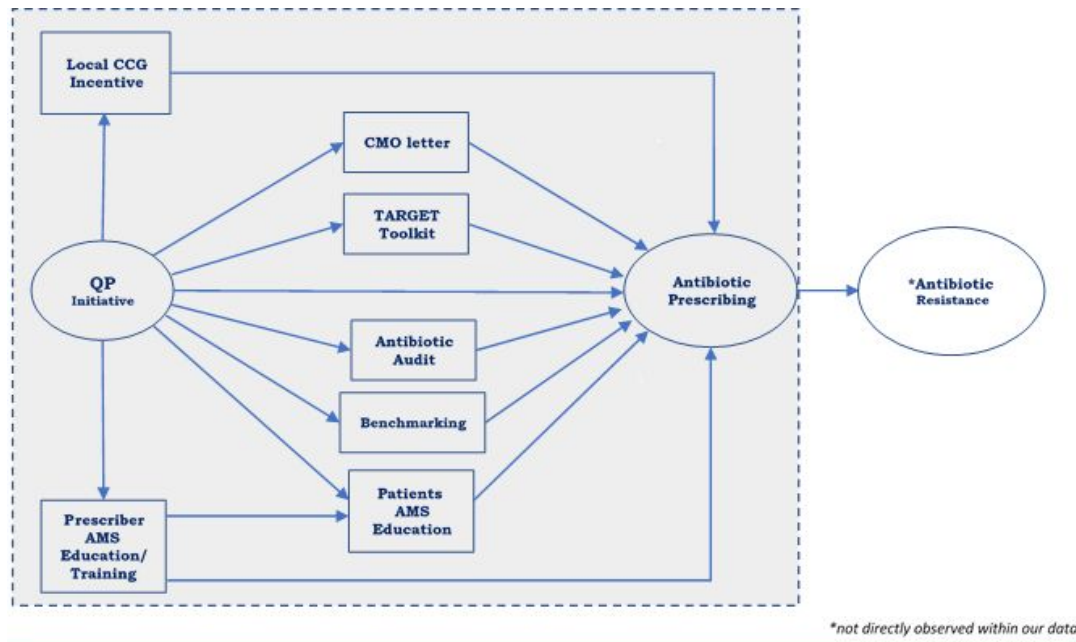
491 **Authors contributions**

492 All authors contributed to the conception and study design. PA and CC developed the analysis
493 plan. The manuscript was drafted by PA with further input from CC, STC and AB. All authors
494 approved the submission of the manuscript.

495 **Competing Interests**

496 None declared.
497

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499 **Fig. 1: Conceptual model.** The direct effect is represented by path between the QP initiative
 500 (predictor) and antibiotic prescribing rate (outcome).

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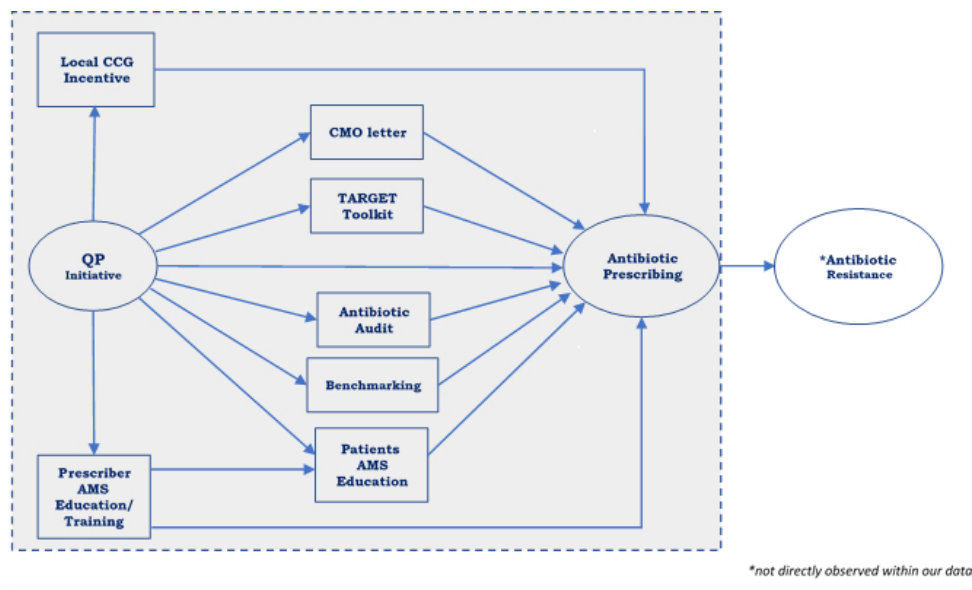


Fig. 1: Conceptual model. The direct effect is represented by the path between the QP initiative (predictor) and antibiotic prescribing rate (outcome).

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Keywords:	Antibiotics, Quality Premium Initiative, Resistance, PRIMARY CARE, Mediation analysis, General practice

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5 2 Initiative on Antibiotic Prescribing in Primary Care Practices in
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7 3 England: A Study Protocol.
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34 **Abstract**

35 **Introduction**

36 The persistent development and spread of resistance to antibiotics remains an important public
37 health concern in the UK and globally. About 74% of antibiotics prescribed in England in 2016
38 was in primary care. The Quality Premium (QP) initiative that rewards Clinical Commissioning
39 Groups (CCGs) financially based on the quality of specific health services commissioned is
40 one of the National Health Service (NHS) England interventions to reduce antimicrobial
41 resistance through reduced prescribing. Emerging evidence suggests a reduction in antibiotic
42 prescribing in primary care practices in the UK following QP initiative. This study aims to
43 investigate the mechanism of impact of this high-cost health-system level intervention on
44 antibiotic prescribing in primary care practices in England.

45 **Methods and analysis**

46 The study will constitute secondary analyses of antibiotic prescribing data for almost all
47 primary care practices in England from the NHS England Antibiotic Quality Premium
48 Monitoring Dashboard and OpenPrescribing covering the period 2013 to 2018. The primary
49 outcome is the number of antibiotic items per Specific Therapeutic group Age-sex Related
50 Prescribing Unit (STAR-PU) prescribed monthly in each practice or CCG. We will first
51 conduct an interrupted time series using Ordinary Least Square regression method to examine
52 whether antibiotic prescribing rate in England has changed over time, and how such changes,
53 if any, are associated with QP implementation. Single and sequential multiple-mediator models
54 using a unified approach for the natural direct and indirect effects will be conducted to
55 investigate the relationship between QP initiative, the potential mediators and antibiotic
56 prescribing rate with adjustment for practice and CCG characteristics.

57 **Ethics and dissemination**

58 This study will use secondary data that are anonymised and obtained from studies that have
59 either undergone ethical review or generated data from routine collection systems. Multiple
60 channels will be used in disseminating the findings from this study to academic and non-
61 academic audiences.

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3 64 **Strengths and Limitations of this study**
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- 6 65 • This study will be the first to evaluate the mechanism of the impact of a financial
7 66 incentive initiative involving Clinical Commissioning Groups to improve antibiotic
8 67 prescribing in primary care practices in England.
9
10 68 • The investigation of multiple mediators in this study will help to identify the
11 69 contributions of multiple strategies in translating the effects of QP while unpacking the
12 70 extent of the effect of specific mediators.
13
14 71 • Due to the limited data on practice-level interventions or strategies that might
15 72 potentially mediate the effect of the QP on antibiotic prescribing, we will not be able to
16 73 extensively investigate the mechanism of QP impact at the practice level.
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18 74 • Nevertheless, extensive investigations will be conducted at CCG level where the
19 75 Quality Premium initiative is implemented, and rewards paid out.
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77 Introduction

78 The persistent development and spread of resistance to antimicrobials, especially antibiotics,
79 remains an important public health concern in the UK¹ and globally.^{2,3} Antimicrobial resistance
80 (AMR) is a major threat to the treatment and control of infectious diseases as drug-resistant
81 infections are characterised by prolonged morbidity, increased risk of disabilities, death, and
82 cost of healthcare.⁴ A 2014 review estimated that consistent increases in AMR would lead to
83 about 10 million deaths per year by 2050.⁵ Inappropriate prescribing and use of antibiotics in
84 healthcare practices, especially primary care, are integral to the development and spread of
85 resistance.^{6,7}

86 About seventy-four per cent of the antibiotics prescribed in England in 2016 was in primary
87 care.⁸ The high rate of antibiotic prescribing in primary care has been associated with increased
88 antimicrobial resistance.⁹ While some of the antibiotics prescribed in primary care settings are
89 appropriate, a substantial proportion are cases where antibiotics are not clinically indicated,
90 such as suspected respiratory tract conditions which can be self-limiting.^{9,10} Uncertainties about
91 diagnosis, (perceived) patient expectations for antibiotics, occupational pressure (e.g.
92 consultation rate) and previous experiences, are some of the identified drivers of
93 overprescribing in primary care practices.¹¹⁻¹⁶

94 Interventions such as antibiotic stewardship programmes, education and training initiatives
95 targeted at prescribers and patients, financial incentives, among others have been implemented
96 in England to reduce antimicrobial resistance through reduced prescribing. In particular, the
97 Quality Premium (QP) is an National Health Service (NHS) England initiative established in
98 2013 to reward Clinical Commissioning Groups (CCGs) financially based on the quality of
99 specific health services considered to be of national or local priority and commissioned over a
100 specific period.¹⁷ Improvement of antibiotic prescribing in primary care was one of the national
101 priorities in the 2015/16 guidance,¹⁸ constituting 10% of the premium awarded from 2016/17
102 to date.^{19,20} Key aspects of the 'improved antibiotic prescribing' priority are reductions in the
103 number of antibiotics prescribed in primary care facilities across England, and in the proportion
104 of broad-spectrum antibiotics prescribed in primary care (2015-2017).¹⁹ Part of the
105 requirements in the 2015/16 QP guidance for demonstrating improved antibiotic prescribing
106 by CCGs was a reduction in the number of antibiotics prescribed in primary care by 1% of the
107 mean value in England in 2013/14 (i.e. 1.61 items per Specific Therapeutic group Age-sex

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3 108 Related Prescribing Unit (STAR-PU)). This was further increased to 4% in the 2016/17
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5 109 guidance.

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8 110 Emerging evidence suggests a reduction in antibiotic prescribing in primary care practices in
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10 111 the UK following the QP initiative.^{21,22} Prescribing data from England shows a reduction of
11
12 112 about 2.7 million antibiotic items between 2014/15 and 2016/17 financial year.²³ Eighty-eight
13
14 113 per cent of the CCGs in England achieved the target of reducing antibiotic prescribing in the
15
16 114 first two years of QP.²¹ Also, there has been a significant reduction in the proportion of broad-
17
18 115 spectrum antibiotics prescription with 83% of the CCGs meeting their target in the first two
19
20 116 years.²¹ Such reductions in antibiotic prescribing would be expected to contribute to reductions
21
22 117 in the development of resistance.²⁴ However, little is known about the mechanisms by which
23
24 118 the QP initiative impacted on antibiotic prescribing in primary care practices.

25
26 119 The impact of interventions on specific outcomes are sometimes explained by a series of
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28 120 events. Potential mediators are important in assessing causal relationships like that between QP
29
30 121 and antibiotic prescribing in primary care practices in England; where a *potential mediator* is
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32 122 a variable that hypothetically mediates the effect of QP on the outcome. The conceptual model
33
34 123 shown in fig.1 demonstrates the hypothesised pathways for the impact of the QP initiative on
35
36 124 antibiotic prescribing, and subsequently AMR. The model is developed based on conceptual
37
38 125 and empirical evidence from existing literature and the results of qualitative and survey studies
39
40 126 conducted as initial stages of the broader STEP-UP (Improving the uptake and Sustainability
41
42 127 of Effective interventions to promote Prudent antibiotic Use in Primary care)²⁵ project that
43
44 128 includes the current study. The conceptual model will be further validated through a
45
46 129 stakeholder workshop with key antibiotic stewardship personnel, primary care prescribers, and
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48 130 CCG representatives.

49
50 131 Our conceptual model suggests that in addition to its direct impact, the QP initiative acts by
51
52 132 stimulating and enhancing the adoption of existing strategies to reduce and optimise antibiotic
53
54 133 prescribing. In investigating the potential pathways connecting QP to reductions in antibiotic
55
56 134 prescribing, we will be examining the hypothesis that factors like the Chief Medical Officer's
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58 135 (CMO) letter, TARGET toolkit, antibiotic auditing, benchmarking, local incentives at CCG
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60 136 level, prescribers and patients' antimicrobial stewardship (AMS) education/training can
137
138 137 transmit part of the influence of the QP initiative to antibiotic prescribing.

138 **[insert fig. 1]**

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3 139 First implemented in September 2014, the CMO letter, which provided social norm feedback
4
5 140 to primary care practitioners in England whose antibiotic prescribing rate was in the top 20%,
6
7 141 reduced antibiotic prescribing by 3.3% in six months in a randomised trial.²⁶ The criteria for
8
9 142 selecting practices that received the letters in the subsequent years changed with the addition
10
11 143 of measures like a change in antibiotic prescribing over time, and whether practices have
12
13 144 previously been sent CMO letter.

14 145 Another important mediator hypothesised in our conceptual model is AMS education/training
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16 146 of prescribers and patients. Educating and training prescribers on the importance of antibiotic
17
18 147 stewardship and ways to promote prudence can help prescribers make better decisions on when
19
20 148 an antibiotic is indicated and can also improve patients' knowledge on the appropriate use of
21
22 149 antibiotics. AMS interventions targeted at patients can improve their knowledge of when
23
24 150 antibiotics are not needed, increase confidence and skills on how to self-care, which can result
25
26 151 in reduced consultations for self-limiting illness and thus reduced antibiotic prescriptions.

27 152 Treat Antibiotics Responsibly, Guidance, Education, Tools (TARGET) is a toolkit developed
28
29 153 by the Public Health England, the Royal College of General Practitioners and other
30
31 154 professional societies to promote prudent antibiotic use among prescribers and patients in
32
33 155 primary care.²⁷ The intervention comprises of multiple resources (patient information leaflets
34
35 156 on infection management and antibiotic use, self-assessment checklist for prescribers,
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37 157 antibiotic audit toolkits, interactive workshop presentations, national antibiotic management
38
39 158 guidance, training resources, and resources for clinical and waiting areas) to provide clinicians
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41 159 and patients with the motivation and skills to use antibiotics prudently.²⁷ A qualitative study
42
43 160 evaluating prescribers' attitude and perception about the TARGET toolkit reported that general
44
45 161 practitioners described it as useful and important in improving their prescribing behaviours and
46
47 162 the expectations of their patients.²⁸ The use of resources like the TARGET antibiotics
48
49 163 workshop have been shown to reduce antibiotic prescribing rate in a randomised controlled
50
51 164 trial.²⁹

52 165 We hypothesise that the implementation of the QP initiative informed the initiation or wider
53
54 166 use of these strategies indicated in the conceptual model as mediators, which will subsequently
55
56 167 influence antibiotic prescribing at primary care practices.

57 168 The implementation of the QP initiative in NHS England constitutes a natural experiment and
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59 169 offers an opportunity to investigate the pre and post-intervention periods to understand the
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170 mechanism of impact of the QP intervention in reducing antibiotic prescribing rates across the

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3 171 whole of primary care.³⁰ Given the ethical and practical constraints in manipulating exposure
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5 172 in such an intervention, a natural experimental design offers a practical approach to understand
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7 173 the overall effect and mechanism of interventions like QP that offer financial incentives for
8
9 174 clinical compliance. The publication of the 2015/16 QP Guidance¹⁸ constitutes the
10
11 175 'intervention', with periods before this as the 'control'.

12 176 **Study Aim and Objectives**

15 177 Using routinely collected population-level datasets on antibiotic prescribing in England, this
16
17 178 study aims to address the research question: What are the mechanisms and mediators of the
18
19 179 impact of a high-cost health-system level intervention, the 'antibiotic prescribing quality
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21 180 premium'? We will investigate the difference in antibiotic prescribing rate pre and post-QP
22
23 181 initiative to establish its direct, indirect (through mediators), and total effects in reducing
24
25 182 antibiotic prescribing in primary care practices in England.

26 183 **Methods and Analysis**

28 184 **Study Design**

30
31 185 Contemporary evaluations of the effectiveness of health policies go beyond estimating their
32
33 186 total effect on outcomes. Mediation analysis decomposes the total effect of an intervention into
34
35 187 separate causal pathways,³¹ enabling an understanding of why and how policies work by
36
37 188 estimating the direct and indirect effects of the exposure.³² We will conduct mediation analyses
38
39 189 investigating the potential mediators of the impact of QP on antibiotic prescribing in primary
40
41 190 care in England, establishing the direct and indirect effects of the QP initiative.

42 191 **Data sources**

44 192 The study will constitute secondary analyses of antibiotic prescribing data from NHS England
45
46 193 covering the period 2013 to 2018. CCGs were established in England in April 2013 following
47
48 194 the Health and Social Care Act 2012.³³ Data on antibiotic prescribing in primary care at CCG
49
50 195 levels will be sourced from the NHS England Antibiotic Quality Premium Monitoring
51
52 196 Dashboard, which is produced by the NHS Business Services Authority (BSA).³⁴ Primary Care
53
54 197 prescribing data is publicly available from the NHS BSA website. The dataset contains the
55
56 198 number of antibiotic items (STAR-PU) prescribed in each CCG from the financial year 2015/16
57
58 199 to 2018/19, with data for October 2018 the latest at the time of this protocol. Data for the period
59
60 200 2013 to 2015 will be mapped to CCG-level from the practice-level data.

1
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3 201 Practice-level antibiotic prescribing data will be sourced from OpenPrescribing, an Evidence-
4
5 202 Based Medicine DataLab project by the University of Oxford. OpenPrescribing publishes
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7 203 monthly antibiotics prescribing data from August 2013, with data for October 2018 the latest
8
9 204 at the time of this protocol. Practice-level antibiotic prescribing data from OpenPrescribing is
10
11 205 not STAR-PU weighted, so the extracted data will be STAR-PU weighted using figures from
12
13 206 the 2013 Item-based age–sex weighting for oral antibacterials,¹⁴ and the number of registered
14
15 207 patients in each age-gender category in a practice for each specific month.

16 208 Overall, the dataset offers coverage of at least three years post-intervention given that antibiotic
17
18 209 prescribing became a QP priority in March 2015. This will be important in investigating the
19
20 210 immediate direct and indirect effects of the QP initiative while giving an insight into the
21
22 211 sustainability of the identified effects (if any) in the long-term.

23 212 **Variables**

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25
26 213 The predictor will be a binary variable indicating the implementation of the QP intervention.
27
28 214 The intervention will include all periods after March 2015 when the 2015/16 QP guidance in
29
30 215 England was published, while the control will be periods prior to this. The primary outcome of
31
32 216 interest is the rates of antibiotic prescribing at CCG level in England, which will be a
33
34 217 continuous variable indicating the number of items (per STAR-PU) prescribed per month.

35 218 To account for differences in practice and CCG characteristics that can contribute to variance
36
37 219 in antibiotic prescribing, we will be adjusting for the number of General Practitioners in each
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39 220 practice (from the NHS Workforce data),³⁵ the index of multiple deprivation (from the
40
41 221 Department for Communities and Local Government),³⁶ prevalence of co-morbidities (asthma,
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43 222 chronic obstructive pulmonary disease (COPD), diabetes, cancer, chronic kidney disease (from
44
45 223 the NHS Quality and Outcomes Framework database)),³⁷ the prescribing rate of other non-
46
47 224 antibiotic drugs (Opioids and Benzodiazepines), and seasonal flu vaccination rate (from Public
48
49 225 Health England).³⁸

50 226 Mediator variables will be derived from the questionnaire data from a Public Health England
51
52 227 (PHE) survey³⁹ with 187 of the 209 AMS leads representing CCGs in England and data from
53
54 228 other organizations that have evaluated the interventions treated as potential mediators in this
55
56 229 study. In the PHE survey, participants were required to complete questionnaire items which
57
58 230 included their adoption of national and local strategies in their respective CCG to enable them
59
60 231 to meet QP targets on antibiotic prescribing in primary care. The mediator variables will be
232 232 binary or continuous variables indicating the adoption of key interventions and intermediaries

233 that are hypothesised to reflect in the integration of the QP guidance in improving antibiotic
234 prescribing in primary care practices.

235 **Handling missing data**

236 Over the period covered by this study (2013-2018), there have been changes in the number of
237 practices and CCGs in England. Some practices have closed, new practices opened, and some
238 CCGs merged over the period; as such we have missing values for some observations. To
239 maximize the use of existing observations, we will retain all observed values in the main
240 analysis and impute the missing values using multiple approaches.⁴⁰ Missing values for the
241 period before a new CCG was formed through merger of pre-existing CCGs will be imputed
242 using the mean value of the CCGs that constitutes the merger; subsequently, these closed CCGs
243 will be dropped from the dataset. Other missing values in this study will be handled using
244 multiple imputation method on Mplus V.8.2. We will run a separate imputation model for the
245 practice and CCG level datasets, the results will be averaged across 20 imputed datasets.
246 Complete case analysis will be conducted as part of the sensitivity analyses for this study to
247 examine the consistency of the results from the imputed set.

248 **Statistical analysis**

249 Our first analysis will be an interrupted time series to investigate whether antibiotic prescribing
250 rate in England has changed over time, and how such changes, if any, are associated with the
251 QP implementation in March 2015. This will be conducted using the Ordinary Least Square
252 regression method⁴¹ to assess whether the 2015/16 QP establishment resulted in a shift in the
253 level and trend in antibiotic prescribing in primary care in England, compared to the period
254 before the intervention. Using the practice-level dataset, a univariate time series with the mean
255 antibiotic items (STAR-PU weighted) prescribed in all primary care practices in England for
256 each month will be conducted using the *ITSA* function on Stata, with *posttrend* specification to
257 show a post-intervention trend. The Cumby-Huizinga general test for autocorrelation will be
258 used for general specification test of serial correlation in the time series data.⁴²

259 A new Quality Premium guideline was implemented each financial year with changes in the
260 prescribing rate target and the proportion that improved prescribing constituted in the QP award
261 for each year. Our mediation analyses will investigate the effects of the QP by comparing
262 antibiotic prescribing rate in the financial year before its implementation to each subsequent
263 year post-implementation; as such our dataset for the mediation analyses will have the control
264 group as the financial year before QP and the intervention group as a specific post-QP

1
2
3 265 implementation year. Three analyses will be conducted for each of the three financial years
4
5 266 since QP establishment. This will enable us to compare the effects of the different target levels
6
7 267 that have been set over the years, and the proportions of the QP award attributed to
8
9 268 improvement in antibiotic prescribing.

10
11 269 Using a unified model for the natural direct and indirect effects,³¹ we will investigate the
12
13 270 relationship between the QP initiative, the potential mediators and antibiotic prescribing rate
14
15 271 with adjustment for the practice and CCG characteristics. This approach addresses the issues
16
17 272 associated with the traditional approach to mediation analysis that obtains natural direct and
18
19 273 indirect effect estimates through a nontrivial combination of parameter estimates from multiple
20
21 274 models for the regression of the mediator and that of the outcome.^{43,44} Also, the unified model
22
23 275 is applicable to nonlinear regressions, different measurement types for outcome and mediator
24
25 276 variables, and allows for interaction between the exposure and the mediator.³¹

26
27 277 We will first fit single-mediator models with each mediator separately modelled using the
28
29 278 *medeff* function in Stata.⁴⁵ With the single-mediator models, we will be able to establish the
30
31 279 individual influence of each potential mediator variable. Variables that showed a mediating
32
33 280 effect in the single mediator models will be added to build a multiple-mediator model using a
34
35 281 sequential mediation analysis method.⁴⁶

36
37 282 A sequential multiple mediators analysis is preferred to merely summing the effects of the
38
39 283 single mediators because this sum may differ from the joint mediated effect; particularly as our
40
41 284 potential mediators may influence one another.⁴⁶ Modelling all the significant mediators
42
43 285 together provides a more accurate assessment of the mediation effects and causal
44
45 286 relationship^{47,48} while assessing the indirect effect of a group of mediators in explaining how
46
47 287 and why the intervention impacts on the outcome. The ordering of the mediators in the
48
49 288 sequential mediation analysis will be based on evidence from the literature and the outcome of
50
51 289 our stakeholders' workshop designed to identify possible pathways between the predictor,
52
53 290 mediators and outcome. The workshop which will validate of our conceptual model, will also
54
55 291 enable us to identify what mediators affect one another and inform interactions to include in
56
57 292 our model. All analysis will be conducted in the Stata statistical package version 15.1.

58 293 **Sensitivity analyses**

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60 294 Sensitivity analyses using dummy implementation dates of one to three months before and after
61
62 295 the actual month each of the QP guidance were published will be conducted to assess the
63
64 296 difference between the time the guidance is published and the dissemination of information

297 and development of local arrangements by the CCGs. These analyses will further help to
298 investigate the anticipatory effect of the policy and whether lag in implementation attenuates
299 the effect of the intervention.

300 Also, we will conduct separate analysis with the outcome variable (antibiotic prescribing rate)
301 as a binary variable (indicating whether each CCG achieved the required rate of reduction in
302 antibiotic prescribing as stated in the QP guidance for each year) to examine whether the
303 classification of the outcome variable based on achievement of QP target influences the results.

304 Subgroup analyses will be conducted on clusters of primary care practices based on their
305 antibiotic prescribing behaviour (high and low prescribers) and indices of deprivation to
306 examine whether any effect of the QP initiative seen in the overall population is different in
307 subgroups of practices. The top and bottom 20% antibiotic prescribers as of March 2015 will
308 be categorised as high and low prescribers. To address the issue of regression to mean in
309 subgroup analyses, we will build a separate model with categorization into high and low
310 prescribers based on the mean of the prescribing rate of practices in the last three months to
311 March 2015. The use of mean of multiple measures will offer a better estimate of each
312 practice's true mean before the 2015/16 Quality Premium initiative.⁴⁹ The subgroup analysis
313 based on the indices of deprivation data^{36,50} at primary-care practice level will be important in
314 establishing the equity impact of the QP initiative.

315 **Limitations**

316 This study has some limitations. The survey that provided data on mediator variables included
317 187 of the 209 CCGs existing as at the time of the study. However, this sample size is large
318 enough for strong statistical power, and multiple imputation will be used to address issues on
319 missingness. Furthermore, due to the limited data on practice-level interventions or strategies
320 that might potentially mediate the effect of the QP on antibiotic prescribing, we will not be able
321 to extensively investigate the mechanism of QP impact at the practice level. Nevertheless,
322 extensive investigations will be conducted at CCG-level where we have more data on potential
323 mediators.

324 In 2013, the Primary Care Trusts (PCTs) in England, which were responsible for planning and
325 commissioning health care services at the primary care level, were transformed to Clinical
326 Commissioning Groups.⁵¹ As such, our investigations are restricted to the CCG era. This is
327 important as the Quality Premium initiative is implemented, and rewards paid out at CCG level.

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2
3 328 We recognise that the causal interpretation of any effect from our mediation analysis rests on
4
5 329 assumptions such as sequential ignorability and exchangeability. Causal inference from this
6
7 330 analysis will be limited given that our data is observational with the absence of random
8
9 331 assignment of cases to treatment and mediator levels, as well as the likelihood of unmeasured
10
11 332 confounders. The rate of consultation for conditions where antibiotics might be prescribed is
12
13 333 one of the unmeasured confounders in our study. This has not been accounted for in our
14
15 334 analyses as this data is not available nationally at the practice level.

16 335 **Discussion**

17
18 336 Although the Quality Premium intervention has been reported to have been effective in
19
20 337 reducing antibiotic prescribing,²² there remain important gaps in the evidence base for this
21
22 338 intervention, especially in relation to its mechanism of impact. This study will be the first to
23
24 339 evaluate the mechanism of the impact of a financial incentive initiative involving CCGs to
25
26 340 improve antibiotic prescribing in primary care practices in England. If our study identifies some
27
28 341 key mediators, like other interventions implemented in similar time or in response to the QP
29
30 342 initiative, that explain the indirect effect of the QP intervention on antibiotic prescribing, this
31
32 343 will provide important evidence on the effectiveness of the implementation of a package of
33
34 344 interventions on antibiotic prescribing. The investigation of multiple mediators in this study
35
36 345 will also help to highlight the contributions of multiple factors in translating the effects of QP
37
38 346 while unpacking the extent of the effect of specific mediators.

39
40 347 Evidence on the mechanism of impact of strategies like QP will be important in improving its
41
42 348 uptake and sustainability while maximizing its potential in reducing antibiotic prescribing in
43
44 349 primary care settings.

45
46 350 Finally, financially-incentivized strategies for clinical compliance have been criticised for their
47
48 351 ability to result in unintended consequences.⁵² In the case of the QP initiative, unintended
49
50 352 consequences like not prescribing antibiotics in cases where they are indicated are possible.
51
52 353 However, some of the QP response strategies that we hypothesised as potential mediators (such
53
54 354 as prescribers' AMS education/training) have the ability to mitigate this unintended
55
56 355 consequence. By comparing the prescribing rate before and after the QP initiative and
57
58 356 identifying the strategies that explain its effect, we will generate evidence that will be important
59
60 357 in considerations of the future of this intervention and revisions that may help reduce potential
358 unintended consequences.

359 **Patient and public involvement**

1
2
3 360 This study will use secondary data mostly from routine collection system and will not directly
4
5 361 involve patients or the public. The dissemination of the results will include communication
6
7 362 channels and public engagement events that will involve primary care practitioners and CCG
8
9 363 representatives.

10 364 **Ethics and dissemination**

11
12
13 365 This study will use secondary data that are anonymised and obtained from studies that have
14
15 366 either undergone ethical review or generated data from routine collection systems. Prescribing
16
17 367 data from NHS BSA and NHS Digital are generated from routinely collected prescribing data
18
19 368 on items that have been dispensed in primary care practices in England. The survey that
20
21 369 produced the data on mediator variables was registered with the Public Health England
22
23 370 Research Support and Governance Office (RSGO) and approved by Public Health England
24
25 371 Research Ethics and Governance Group (REGG) and Health Research Association (HRA).

26 372 Multiple channels will be used in disseminating the findings from this study to academic and
27
28 373 non-academic audiences. With will include an engagement workshop with our stakeholder
29
30 374 network, presentations in scientific conferences, publication in peer-reviewed journals, press
31
32 375 conference coinciding with paper publications.

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43
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49
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51 385 **Authors contributions**

52
53 386 All authors contributed to the conception and study design. PA and CC developed the analysis
54
55 387 plan. The manuscript was drafted by PA with further input from CC, STC and AB. All authors
56
57 388 approved the submission of the manuscript.

58 389 **Competing Interests**

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2
3 390 None declared.
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5
6 391 **Data sharing statement**
7

8 392 This study will use secondary data that is publicly available to bona fide researchers. The data
9
10 393 from the Public Health England survey can be sourced from the organization.
11

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Fig. 1: Conceptual model. The direct effect is represented by the path between the QP initiative (predictor) and antibiotic prescribing rate (outcome).

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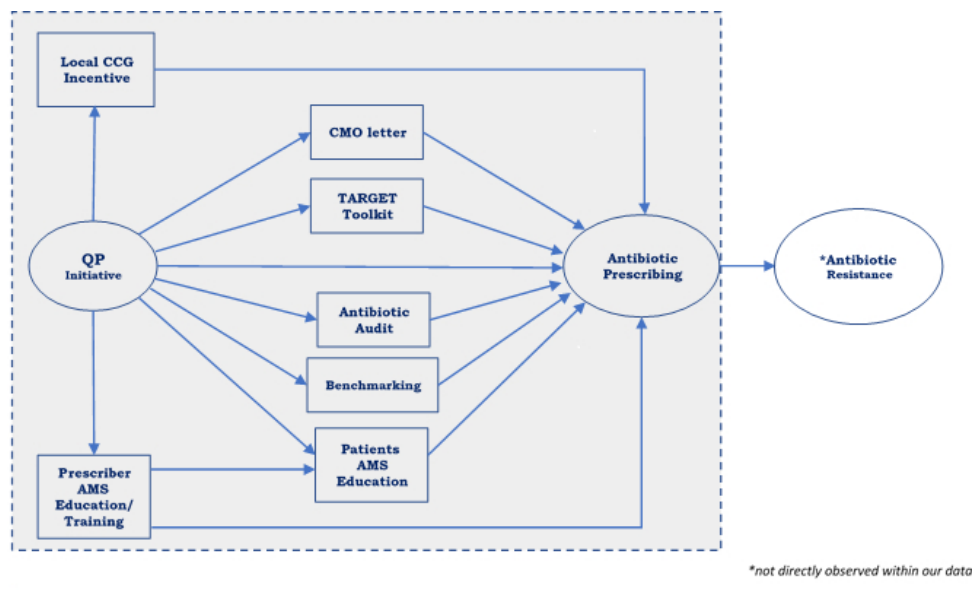


Fig. 1: Conceptual model. The direct effect is represented by the path between the QP initiative (predictor) and antibiotic prescribing rate (outcome).