An assessment of potential unintended consequences following a national antimicrobial stewardship programme in England: an interrupted time series analysis.

Violeta Balinskaite, research associate[1]; Sabine Bou-Antoun, PhD student[3,4]; Alan P. Johnson, professor of epidemiology and public health [2,4]; Alison Holmes, professor of infectious diseases[3]; Paul Aylin, professor of epidemiology and public health[1,3,4]

[1]Dr Foster Unit, Department of Primary Care and Public Health, Imperial College London, London, United Kingdom,

[2] National Infection Service, Public Health England, London, United Kingdom,

[3]Department of Primary Care and Public Health, Imperial College London, London, UK

[4]NIHR Health Protection Research Unit in Healthcare Associated Condition and Antimicrobial Resistance, Imperial College London, London, United Kingdom

Corresponding Author: Violeta Balinskaite, Department of Primary Care and Public Health, School of Public Health, Imperial College London, London (v.balinskaite@imperial.ac.uk)

Summary: This study aimed to evaluate possible unintended clinical outcomes related to antimicrobial program with financial incentive. This study shows that overall there was no significant association between the intervention and unintended clinical consequences in primary and secondary care.

ABSTRACT

Background: The 'Quality Premium' (QP) introduced in England in 2015 aimed to financially reward local healthcare commissioners for targeted reductions in primary care antibiotic prescribing. We aimed to evaluate possible unintended clinical outcomes related to this QP.

Methods: Using Clinical Practice Research Datalink and Hospital Episode Statistics datasets, we examined general practitioner (GP) consultations (visits) and emergency hospital admissions related to a series of pre-defined conditions of unintended consequences of reduced prescribing. Monthly age and sex-standardised rates were calculated using a direct method of standardisation. We used segmented regression analysis of interrupted time series to evaluate the impact of the QP on seasonally adjusted outcome rates.

Results: We identified 27,334 GP consultations and over five million emergency hospital admissions with pre-defined conditions. There was no evidence that the QP was associated with changes in GP consultation and hospital admission rates for the selected conditions combined. However, when each condition was considered separately, a significant increase in hospital admission rates was noted for quinsy, and significant decreases were seen for hospital-acquired pneumonia, scarlet fever, pyelonephritis and complicated urinary tract conditions. A significant decrease in GP consultation rates was estimated for empyema and scarlet fever. No significant changes were observed for other conditions.

Conclusions: Findings from this study show that overall there was no significant association between the intervention and unintended clinical consequences, with the exception of a few specific conditions, most of which could be explained through other parallel policy changes or should be interpreted with caution due to small numbers.

Keywords: antimicrobial stewardship programs, antibiotic prescribing, unintended consequences, primary and secondary care, interrupted time series

Introduction

Antimicrobial resistance (AMR) is a serious public health problem threatening to undermine modern medicine [1]. Prescribing and consumption of antibiotics is a key driver of resistance and there have been a number of antimicrobial stewardship programs (pay-for-performance, educational, audits, and guidelines) implemented in different countries with the intention of reducing inappropriate antimicrobial prescribing [2-10].

In the United Kingdom (UK) since the late 1990s, there have been various seasonal campaigns to reduce antibiotic prescribing [11]. However, the number of antimicrobial items dispensed over the period 2002-2012 increased by 17.1% [12]. In England, delivery of healthcare was reorganised in 2012, with the formation of Clinical Commissioning Groups (CCGs) which are clinically-led statutory bodies responsible for the planning and commissioning of health care services for their local area. In 2015, a 'Quality Premium' (QP) was published which aimed to financially reward CCGs for reducing unnecessary antibiotic prescribing in primary care, [13]. We have already demonstrated that this intervention was associated with a significant decrease in all antibiotic items prescribed and in broad-spectrum antibiotic items prescribed (V Balinskaite, AP Johnson et al., submitted manuscript).

In this study, we established a method of surveillance of unintended consequences resulting from measures to reduce antibiotic prescribing. We hypothesised that the reduction in antibiotic prescribing following the introduction of the QP might increase the number of general practitioner consultations and hospital admissions associated with complications arising from pre-defined infections that may have been untreated, and we aimed to assess any such effect using interrupted time series (ITS) analysis.

Methods

Study design and setting

We defined a range of conditions based on the hypothesis that the initial uncomplicated presentation in primary care might be thought to be self-limiting and therefore not treated with antibiotics. These cases may progress to these more severe conditions [14]. A list of Read codes (the standard clinical terminology system used in general practice in the UK) and ICD-10 (the International Classification of Diseases, 10th edition) codes were compiled following a systematic search of the Read codes and Read terms in the Clinical Practice Research Datalink (CPRD) code browser, a search of the published literature on the CPRD website and a short literature review, respectively. The finalised codes for both data sources were independently reviewed by an academic GP (Supplement Tables 1-2). We selected diagnoses related to complications of both respiratory tract infection (community-acquired pneumonia [CAP], hospital-acquired pneumonia [HAP], mastoiditis, quinsy (peritonsillar abscess), meningitis, brain abscess, empyema, scarlet fever and rheumatic fever) and urinary tract infection (pyelonephritis). We also selected specific clinical syndromes that may arise from an initial uncomplicated infection including complicated intra-abdominal infection (cIAI), complicated skin and skin structure infection (cSSSI), complicated urinary tract infection (cUTI) and sepsis.

Data sources

We used datasets from the CPRD and Hospital Episode Statistics (HES). The CPRD is an administrative database of computerised medical records from a representative sample (~7%) of GPs across the UK [15-17]. It includes records of clinical events (medical diagnosis), referrals to specialists and secondary care settings, prescriptions issued in primary care, records of immunisations and vaccinations, diagnostic testing and lifestyle-related information (for example, smoking and alcohol status). We used a standardised hierarchical classification system of Read codes to identify patients

who had a recorded diagnosis, symptom or process of care in the CPRD dataset related to the conditions of interest. CPRD flag GP practices and patients as having acceptable data where data has been verified and meets required CPRD data quality criteria. For this analysis, we included data from "up to standard" GP practices in England and patients who had been flagged as having acceptable records [17]. We extracted data covering the period April 2010 to December 2016, comprising five years before the QP was implemented and 21 months post-QP(being the most recent data available at the time of analysis).

HES is an administrative database which includes information on all inpatients admitted to English National Health Service (NHS) hospitals. Each record contains data on patients' demographics (e.g., sex, age, and ethnicity), the episode of care (for example, trust name, date of admission) and clinical information. Diagnoses were recorded in HES using the International Classification of Diseases, 10th edition (ICD-10). Each patient episode was linked within a 'spell' (admission to one provider) and spells were linked into 'superspells', combining any inter-hospital transfers. We examined seven years and five months of HES data (April 2010 – August 2017): five years before the Quality Premium guidance was implemented and 29 months post Quality Premium.

Intervention

'*The Quality Premium: 2015/16 guidance for CCGs*' was published in April 2015 with the intention of rewarding CCGs in England for improvements in the quality of the services that they commission [13, 18-19]. One of the measures was intended to improve antibiotic prescribing in primary care. We have shown in a previous paper a significant 8.2% decrease in all antibiotic items prescribed and a significant 18.9% decrease in broad-spectrum antibiotic items prescribed associated with the introduction of the Quality Premium (V Balinskaite, AP Johnson et al., submitted manuscript).

Outcomes

We examined GP consultations rates for each of our predefined diagnosis groups before and after the introduction of the QP.

The main outcome of interest in secondary care was hospital admissions; these data were extracted based on ICD-10 codes for our pre-specified condition in the primary diagnosis field. The secondary outcomes were 30-day in-hospital mortality rates, 28-day emergency readmission rates, and long inpatient stay rates (long inpatient stay was defined as above the upper quartile of the length of stay for all years combined) related the clinical condition syndromes (CAP, cIAI, cSSSI, cUTI, sepsis).

Statistical analyses

We calculated monthly age and sex-standardised rates and 95% confidence intervals (CIs) with six age bands (0-14, 15-44, 45-64, 65-74, 75-84, and 85+) using the direct method of standardisation [20]. For primary care consultations we used monthly age and sex-standardised GP consultation rates per million person-months for all conditions as a whole group, and individually, using age- and sex-specific denominators based on patients registered with CPRD practices during the same time period. For secondary care, we used monthly age and sex-standardised admission rates per million population for all conditions combined, and separately, using mid-year population estimates from the Office for National Statistics and the 2001 census as the standard population. Age and sex-observed rates per 1000 admissions for other outcomes (seven-day in-hospital mortality, 28-day emergency readmission and long inpatient stay) were calculated using the number of hospital admissions as a denominator.

We used segmented regression analysis of ITS data to evaluate the impact of the QP on seasonally adjusted outcomes rates (described in detail V Balinskaite, AP Johnson et al., submitted manuscript).

It is well known that age is the risk factor for mastoiditis, meningitis and scarlet fever, and is more common among children. We performed a subgroup analysis for mastoiditis, meningitis, rheumatic

and scarlet fever for children age 0-14. As a control group, we analysed hospital admissions for diabetes and dementia (excluding those with a mention of condition), given that introduction of the 2015/16 QP should have had no effect on these diseases.

In April 2017, new clinical coding standards were implemented, which recommended recording sepsis if present in the primary diagnosis [21]. We hypothesised this would dramatically increase the number of hospital admissions related to sepsis. Therefore a sensitivity analysis was conducted for only 24 months post-intervention period, excluding data from April 2017.

Additional analysis for some of the rarer conditions (mastoiditis, brain abscess and scarlet fever) was carried out by aggregating months into quarters. This allowed a sufficient number of cases per time point, to achieve more robust estimates of change.

All statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

Between April 2010 and December 2016, we identified 27,334 GP consultations with our selected diagnosis groups. Over thirty-four per cent of all consultations were related to CAP (34.4%), followed by pyelonephritis (24.7%) and scarlet fever (19.5%). More than half of the population were 64 years or younger (73.9%) and female (62.0%) (Table 1, Supplement Tables 3). Scarlet fever was most common (83.4%) in children age 0-14. A clear seasonal pattern was observed for CAP and scarlet fever. The seasonal pattern was also seen for all selected conditions combined, though this overall pattern may be driven by CAP and scarlet fever (Supplement Table 4). The segmented regression model showed that the standardised GP consultation rates, combining the change in level and the change in slope, did not change significantly over the study period for all the selected conditions combined (change in level: -3.623, P=0.64; change in slope: 0.327, P=0.86) (Table 2, Figure 1). Although there was no significant change in level and in slope in the age and sex-standardised GP consultation rates, looking at each condition separately, a significant decrease in relative change was

estimated for empyema by -86.8% (95%CI -127.6% to -46.1%) and scarlet fever by -26.7% (95%CI -48.6% to -4.8%), indicating approximately 1,219 and 13,736 fewer GP consultations during the 21 month period after the QP was introduced, respectively. No significant change was observed for other conditions.

We identified 5,103,733 emergency hospital admissions using our pre-defined conditions ICD-10 codes in the primary diagnosis between April 2010 and August 2017. Nearly thirty per cent of all admissions were cUTIs (28.1%), followed by CAP (27.8%) and cSSSIs (21.6%). More than half of the population were 65 years or older (54.4%) and female (52.7%) (Supplement Tables 3-4). Mastoiditis, meningitis, scarlet fever and rheumatic fever were more common in children age 0-14. The seasonal pattern was present in all conditions, except for brain abscess and rheumatic fever (Supplement Tables 5). The age and sex-standardised hospital admission rates for CAP and HAP were highest during the winter period, while standardised hospital admission rates for pyelonephritis reached a peak in late summer/early autumn. After the QP had been implemented, the segmented regression model showed no significant drop in level for all conditions combined; however, a significant change in slope (change in trend) was obtained. There was no statistically significant relative change (0.7%, 95%CI -3.9% to 5.4%), representing 13,623 (95%CI -70,052 to 97,282) more hospitals admissions during the 29 post-intervention months compared with the expected number of hospital admissions based on the trend in the pre-intervention period (Table 2, Figure 2). There was no significant change in standardised hospital admission rates for CAP, mastoiditis, meningitis, empyema, rheumatic fever, cIAIs , cSSSIs and sepsis. The standardised hospital admission rates significantly increased for quinsy by 8.3% (95%CI 2.7% to 13.9%). However, a significant decrease in standardised hospital admission rates was observed for HAP by 9.2% (95%CI -17.1% to -1.3%), scarlet fever by 28.0% (95%CI -45.6% to -10.5%), pyelonephritis by 12.2% (95%CI -16.9% to -7.4%) and cUTIs by 22.4% (95%CI -32.2% to -12.5%) (Table 2, Figures 3-5, Supplement Figures 1-4). In our subgroup analysis, we found a significant decrease in age and sex-standardised hospital admission rates for

children age 0-14 for meningitis (-21.0%; 95%CI -39.9 to -9.1) and scarlet fever by (-22.9%; 95%CI -44.5% to -1.3%); and no significant change for mastoiditis and rheumatic fever (Supplement Table 5). Furthermore, a significant change was estimated for the control group.

During the same study period, there was no significant change in the age and sex-standardised 30-day in-hospital mortality rates for CAP, cIAI, cSSSI, cUTI and sepsis (Supplement Table 6). A significant increase in standardised 28-day emergency readmission rates was estimated for cSSSIs. The age and sex standardised long inpatient stay significantly increased for sepsis; though there was a significant decrease in other clinical condition syndromes.

Sensitivity analysis

For the sensitivity analysis, we also performed a second segmented regression analysis including only 24 months after the intervention (Supplement Table 7). This analysis showed no significant change in standardised hospital admission rates for HAP and a significant increase for mastoiditis, cIAIs and sepsis. For the remaining conditions, similar results were found compared with the 29 month analysis after the intervention. An additional analysis of rare conditions by quarter showed a significant increase in standardised hospital admission rates for mastoiditis and a significant decrease for scarlet fever; however, no significant changed were observed for brain abscess (Supplement Table 8).

Discussion

In our analysis, we found no significant association between the QP and GP consultation rates for all the selected conditions combined. No significant association was observed between the QP and hospital admission rates for all the selected conditions and complications combined.

Our study is the first to investigate the association between the QP and adverse clinical outcomes in primary and secondary care, and to our knowledge, the first study in the globe to evaluate the potential unintended consequences of a national antimicrobial stewardship initiative with a financial

incentive However, there are several studies which have looked at the association between antimicrobial stewardship programs with no financial initiatives (educational and guidelines) and adverse outcome, and found mixed results [22-24]. A study in Wales looked at the association between a multifaceted educational programme (with no financial initiatives) and adverse outcome. The authors, using a practice-based randomised controlled trial, found no significant differences in re-consultation rates and hospital admissions for respiratory tract condition between practices which received an educational programme and control practices which provided usual care [22]. Our study included an analysis of the complications of respiratory tract conditions, and similar results were found. A recent retrospective study in Italy investigated the impact of the Italian paediatric guidelines for the treatment of acute otitis media found no association between new guidelines and the number of cases of mastoiditis [23]. Also in this study, the authors did not find any changes in antibiotic prescribing after the guidelines were implemented. Furthermore, a descriptive statistic was used to determine associations. Using ITS analysis, we found no significant change in hospital admissions for mastoiditis for children age 0-14. While another study in Scotland looked at the association between the antimicrobial stewardship programme and unintended harm resulting in hospital admissions for peritonsillar abscess, mastoiditis and community-acquired pneumonia [24]. Authors found no evidence reduction in unnecessary antibiotic use has resulted in patients with serious respiratory tract conditions.

The main strength of this study is the use of a large and rich national administrative hospital and GP datasets. Another strength is the use of an ITS design to assess the impact of the QP. ITS is the strongest quasi-experimental research design and is very useful when a randomised control trial (RCT) is either not feasible or unethical. Segmented regression analysis is a useful statistical method which addresses important threats to internal validity by making multiple assessments of the outcome variable both before and after the intervention. It can estimate the size of the association at different time points, as well as changes in the trend of the association over time. Though there is

a concern around HES data quality of the primary and secondary diagnosis and procedure fields, a recent systematic review of discharge coding accuracy in UK data found that primary diagnosis accuracy has improved since the introduction of Payment by Results in 2002 [25]. The review showed that the primary diagnoses accuracy improved significantly from 73.85 to 96.0% and concluded that routinely collected data are sufficiently robust. Furthermore, submission of HES records is mandatory and, in general, coverage is very high [26].

There are several limitations that need to be considered when interpreting the findings. First, a longer post-intervention period for GP consultations would adequately include seasonal variation (minimum 24-time points after intervention) and might allow a sufficient number of observations per time point, by aggregating months into quarters (a minimum of 100 cases is desirable)[27]. However, fulfilling the latter condition for meningitis/brain abscess and empyema is not practical, even with a longer post-intervention period, due to the small number of GP consultations per year. Furthermore, a post-intervention period longer than 24 months is needed for quinsy, in order to have a sufficient number of GP consultations per time point. Secondly, there have been multiple national and local interventions and change in management during the study period. CCGs started to manage tonsillectomy as an individual funding request, and according to summary reports on inpatient activities (from NHS Digital), there was a decrease in procedures related to 'excision of tonsils' from 2015/16. In other research, it has been shown that a decrease in the rate of tonsillectomy in England and Wales was associated with an increase in hospital admissions with tonsillitis [28-29].

For sepsis, there was a parallel national intervention that was introduced (Commissioning for Quality and Innovation [CQUIN] Guidance for 2015/16) which provided financial incentives for hospitals to undertake certain actions. Two new indicators were introduced relating to the identification and early treatment of sepsis. This raised the rate of screening for sepsis among Emergency Departments

from 52% to 80%. New clinical coding standards were implemented in April 2017, which recommended recording sepsis in the primary diagnosis if present [21]. This is likely to account for the jump in trend in the last few months of observation (Figure 5).

Finally, our study was not able to identify a causal relationship between the QP and hospital admissions rates. It is difficult and rarely possible to do RCTs to evaluate the impact of policy changes. However, observational studies based on ITS analyses are a valid approach.

Conclusions

In conclusion, we find no significant association between a national antimicrobial stewardship programme and unintended clinical consequences in primary and secondary care, with the exception of a few specific conditions, most of which could be explained through other parallel policy changes or should be interpreted with caution due to small numbers. This observational study can never identify a causal relationship between the QP and possible unintended clinical outcomes; however, our findings can perhaps reassure patients, GPs and policymakers that reducing unnecessary antibiotic prescriptions in primary care does not appear to be associated with an overall increase in unintended clinical outcomes. We believe these findings may also be of interest to other countries implementing similar stewardship programmes. However, continued surveillance is necessary to monitor the effects of future national interventions to reduce antibiotic prescribing and further work is required to examine whether specific groups of patients are more at risk of unintended consequences.

Notes

Author contributions. VB, AJ, AH and AP contributed to the original research proposal and helped refine the classification of outcomes used, and the procedure groups for further analysis. SBA prepared the ISAC protocol for CPRD and provided the initial CPRD Read code lists. VB carried out the analysis. VB and PA wrote the first draft, and all authors commented on subsequent drafts of the manuscript.

Acknowledgement. We would like to thank Dr Benedict Hayhoe for his input into finalising Read code list and also we would like to thank Fran Husson and Tim Sims for their contribution towards Independent Scientific Advisory Committee (ISAC) protocol.

Disclaimer. The views expressed in this article are those of the authors and do not necessarily represent the position of the funder. The findings achieved herein are solely the responsibility of the authors.

Financial support. This work was supported by the NIHR Policy Research Programme (Research to determine the impact of the national antimicrobial stewardship programmes on clinical outcomes and patient safety and establish sustainable systems). The views expressed in this publication are those of the authors. The Dr Foster Unit is an academic unit in the Department of Primary Care and Public Health, within the School of Public Health, Imperial College London. The unit receives research funding from the National Institute of Health Research and Dr Foster Intelligence, an independent health service research organisation (a wholly owned subsidiary of Telstra). This work was by supported by the

National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Healthcare Associated Conditions and Antimicrobial Resistance at Imperial College London in partnership with Public Health England (PHE). The Dr Foster Unit at Imperial is affiliated with the National Institute of Health Research (NIHR) Imperial Patient Safety Translational Research Centre. The NIHR Imperial Patient Safety Translational Centre is a partnership between the Imperial College Healthcare NHS Trust and Imperial College London. The Department of Primary Care & Public Health at Imperial College London is grateful for support from the NW London NIHR Collaboration for Leadership in Applied Health Research & Care (CLAHRC) and the Imperial NIHR Biomedical Research Centre.

Potential conflicts of interest. All authors have submitted the ICMJE form for disclosure of potential conflicts of interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Dr. Holmes is Director of NIHR HPRU in HCAI and AMR and a Professor at Imperial College London; Dr. Holmes also received an honorarium for presenting at conference entitled South African Antibiotic Stewardship Programme Annual Workshop, sponsored by Merck (MSD Hoddesdon), outside the submitted work. Dr. Aylin reports grants from Dr Foster (A wholly owned subsidiary of Telstra Health) and grants from NIHR, received during the conduct of the study. Dr. Balinskaite reports grants from The Department of Health, during the conduct of the study. All other authors have no conflicts of interest to declare.

Ethical approval. The principal investigator has approval from the Secretary of State and the Health Research Authority under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 to hold confidential data and analyse them for research

purposes (CAG ref 15/CAG/0005). We have the approval to use them for research and measuring quality of delivery of healthcare from the London-South East Ethics Committee (REC ref 15/LO/0824). The research protocol for the use of CPRD was approved by the ISAC for Medicines and Healthcare products Regulatory Agency (MHRA) database research (protocol number 16_129R).

Reference

1. O'Neill J. Securing new drugs for future generations: the pipeline of antibiotics. Review on antimicrobial Resistance, May 2015
2. Yip W, Powell-Jackson T, Chen W, et al. Capitation combined with pay-for-performance improves antibiotic prescribing practices in rural China. *Health Affairs* **2014**; 33: 502-510
3. Mullen KJ, Frank RG, and Rosenthal MB. Can you get what you pay for? Pay-for-performance and the quality of healthcare providers. *Rand J Economics* **2010**; 41:64-91
4. Ellegård LM, Dietrichson J, and Anell A. Can pay-for-performance to primary care providers stimulate appropriate use of antibiotics? *Health Economics* **2017**; DOI:10.1002/hec.3535
5. Bou-Antoun S, Costelloe C, Honeyford K, et al. Age-related decline in antibiotic prescribing for uncomplicated respiratory tract conditions in primary care in England following the introduction of a national financial incentive (the Quality Premium) for health commissioners to reduce use of antibiotics in the community: an interrupted time series analysis. *J Antimicrob Chemother* **2018**, dky237
6. Butler CC, Simpson SA, Dunstan F, et al. Effectiveness of multifaceted educational programme to reduce antibiotic dispensing in primary care: practice based randomised controlled trial. *BMJ* **2012**; 344: d8173

7. Gerber JS, Prasad PA, Fiks AG, et al. Effect of an outpatient antimicrobial stewardship intervention on broad-spectrum antibiotic prescribing by primary care paediatricians. *JAMA* **2013**; 309: 2345-2352
8. Hemkens LG, Saccilotto R, and Reyes SL. Personalized prescription feedback using routinely collected data to reduce antibiotic use in primary care: a randomized clinical trial. *JAMA Int Med* **2017**; 177:176-183
9. Mölstad S, Erntell M, Hanberger H, et al. Sustained reduction of antibiotic use and low bacterial resistance: 10-year follow-up of the Swedish Strama programme. *Lancet Infect Dis* **2008**, 8: 125-132
10. Van der Velden AW, Pijpers EJ, Kuyvenhoven MM, et al. Effectiveness of physician-targeted interventions to improve antibiotic use for respiratory tract conditions. *Br J Gen Pract* **2012**; 62(605): e801-807
11. Collier J, Foster J. Management of a restricted drugs policy in hospital: the first five years' experience. *Lancet* **1985**; 325: 331-3
12. NHS Digital. Prescriptions Dispensed in the Community, statistics for England: 2002-2012.
13. NHS England. Quality Premium: 2015/16 guidance for CCGs, 21 September 2015 (https://www.england.nhs.uk/wp-content/uploads/2013/12/qual-prem-guid.pdf)
14. Gulliford MC, Moore MV, Little P, et al. Safety of reduced antibiotic prescribing for self limiting respiratory tract conditions in primary care: cohort study using electronic health records. *BMJ* **2016**; 354:i3410
15. Kousoulis AA, Rafi I, de Lusignan S. The CPRD and the RCGP: building on research success by enhancing benefits for patients and practices. *B J Gen Pract* **2015**; 65: 54-55
16. Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al. Validity of the general practice research database. Pharmacotherapy: *Human Pharmacol and Drug Therapy* **2003**; 23:686-689

17. Herret E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* **2015**; 44: 827-836
18. Naylor C, Curry N, Holder h, et al. Clinical commissioning groups. Supporting improvement in general practice? The King's fund 2013 (https://www.kingsfund.org.uk/sites/default/files/field/field_publication_file/clinical-commissioning-groups-report-ings-fund-nuffield-jul13.pdf)
19. Li G, Hooper C, Papanikitas A, et al. The ethics of setting national antibiotic policies using financial incentives. *Brit J Gen Pract* **2017**; 67: 419-420
20. Naing NN. Easy way to learn standardization: Direct and indirect methods. *Malaysian J Med Sci* **2000**; 7:10-15
21. NHS Digital. Coding Clinic, March 2017 (file:///C:/Users/vbalinsk/Desktop/Coding_Clinic_032017_V6.2.pdf)
22. Butler CC, Simpson SA, Dunstan F, D et al. Effectiveness of multifaceted educational programme to reduce antibiotic dispensing in primary care: practice based randomised controlled trial. *BMJ* **2012**; 344: d8173
23. Palma S, Rosafio C, Del Giovane C, et al. The impact of the Italian guidelines on antibiotic prescription practices for acute otitis media in a paediatric emergency setting. *Ital J Ped* **2015**; 41:37
24. NHS National Services Scotland Information Services Division. NHS National Services Scotland Information Services Division. Measuring Potential Unintended Consequences of Reducing Primary Care Antimicrobial Prescribing Unig NHS Scotland's Condition Intelligence Platform (http://www.isdscotland.org/Health-Topics/Health-and-Social-Community-Care/Condition-Intelligence-Platform/Communications/_docs/20162709_Poster_7b.pdf)
25. Burns EM, Rigby E, Mamidanna R, et al. Systematic review of discharge coding accuracy. *J Pub Health* **2011**; 34:138-148

26. HSCIC. NHS Hospital Data and Datasets: A Consultation. 22 July 2013

27. Wagner AK, Soumerai SB, Zhang F, et al. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther* **2002**;27:299-309

28. Mcleod R, Brahmabhatt P, Owens D. Tonsillectomy is not a procedure of limited value–the unseen costs of tonsillitis and quinsy on hospital bed consumption. *Clinical Otolaryngology* **2017**; 42:573-577

29. Al-Hussaini A, Owens D, Tomkinson A. Health costs and consequences: have UK national guidelines had any effect on tonsillectomy rates and hospital admissions for tonsillitis? *European Arch Oto-Rhino-Laryngology* **2013**; 270:1959-1965

Table 1 The total numbers and proportion (%) of general practitioner consultations and emergency hospital admissions in England by age, sex and infection group

Conditions	Total	Age						Sex
		0-14	15-44	45-64	65-74	75-84	85+	Female
Primary care (CPRD)								
All infections	27,334 (100)	5,982 (21.9)	8,693 (31.8)	5,524 (20.2)	2,404 (8.8)	2,358 (8.6)	2,373 (8.7)	16,956 (62.0)
Community acquired pneumonia	9,391 (34.4)	559 (6.0)	1,492 (15.9)	2,096 (22.3)	1,360 (14.5)	1,735 (18.5)	2,149 (22.9)	4,987 (53.1)
Mastoiditis	3,479 (12.7)	609 (17.5)	1,113 (32.0)	986 (28.3)	398 (11.4)	271 (7.8)	102 (2.9)	2,113 (60.7)
Quinsy	1,968 (7.3)	140 (7.1)	1,444 (73.4)	307 (15.6)	55 (2.8)	16 (0.8)	6 (0.3)	957 (48.6)
Meningitis/brain abscess	186 (0.7)	46 (24.7)	61 (32.8)	45 (24.2)	17 (9.1)	11 (5.9)	6 (3.2)	103 (55.4)
Empyema	208 (0.8)	11 (5.3)	54 (26.0)	65 (31.3)	31 (14.9)	29 (13.9)	18 (8.7)	67 (32.2)
Scarlet fever	5,336 (19.5)	4,449 (83.4)	634 (11.9)	170 (3.2)	46 (0.9)	28 (0.5)	9 (0.2)	2,828 (53.0)
Pyelonephritis	6,738 (24.7)	165 (2.4)	3,888 (57.7)	1,849 (27.4)	493 (7.3)	263 (3.9)	80 (1.2)	5,889 (87.4)
Secondary care (HES)								
All infections	5,103,733 (100)	352,091 (6.9)	1,037,852 (20.3)	936,776 (18.4)	735,706 (14.4)	1,045,926 (20.5)	995,382 (19.5)	2,690,007 (52.7)
Community	1,419,093	77,270	101,179	210,837	249,751	389,352	390,704	701,381

acquired pneumonia	(27.8)	(5.4)	(7.1)	(14.9)	(17.6)	(27.4)	(27.5)	(49.4)
Hospital acquired pneumonia	178,911 (3.5)	4,835 (2.7)	9,211 (5.1)	26,767 (15.0)	32,816 (18.3)	51,888 (29.0)	53,394 (29.8)	86,577 (48.4)
Mastoiditis	5,341 (0.1)	3,343 (62.6)	1,036 (19.4)	508 (9.5)	199 (3.7)	160 (3.0)	95 (1.8)	2,487 (46.6)
Quinsy	55,835 (1.1)	2,155 (3.9)	44,250 (79.3)	7,903 (14.2)	1,065 (1.9)	366 (0.7)	96 (0.2)	23,684 (42.4)
Meningitis	13,690 (0.3)	5,646 (41.2)	3,941 (28.8)	2,447 (17.9)	960 (7.0)	523 (3.8)	173 (1.3)	6,840 (50.0)
Brain abscess	3,265 (0.1)	424 (13.0)	904 (27.7)	1,118 (34.2)	483 (14.8)	263 (8.1)	73 (2.2)	1,152 (35.3)
Empyema	9,772 (0.2)	705 (7.2)	1,719 (17.6)	3,118 (31.9)	2,075 (21.2)	1,540 (15.8)	615 (6.3)	2,974 (30.4)
Scarlet fever	5,300 (0.1)	5,118 (96.6)	163 (3.1)	16 (0.3)	1 (<0.1)	2 (<0.1)	0 (0.0)	2,439 (46.0)
Rheumatic fever	325 (<0.1)	154 (47.4)	77 (23.7)	44 (13.5)	18 (5.5)	25 (7.7)	7 (2.2)	169 (52.0)
Pyelonephritis	170,297 (3.3)	8,511 (5.0)	100,324 (58.9)	36,330 (21.3)	13,132 (7.7)	8,868 (5.2)	3,132 (1.8)	142,639 (83.8)
Complicated intra-abdominal infections	300,948 (5.9)	21,939 (7.3)	124,113 (41.2)	85,462 (28.4)	32,934 (10.9)	24,990 (8.3)	11,510 (3.8)	126,372 (42.0)
Complicated	1,100,167	85,983	345,678	286,266	143,278	141,082	97,880	525,791

skin and skin structure infections	(21.6)	(7.8)	(31.4)	(26.0)	(13.0)	(12.8)	(8.9)	(47.8)
Complicated urinary tract infections	1,432,424 (28.1)	103,669 (7.2)	269,574 (18.8)	190,998 (13.3)	176,269 (12.3)	331,127 (23.1)	360,787 (25.2)	863,122 (60.3)
Sepsis	408,365 (8.0)	32,339 (7.9)	35,683 (8.7)	84,962 (20.8)	82,725 (20.3)	95,740 (23.4)	76,916 (18.8)	204,380 (50.0)
Diabetes	243,322	33,130 (13.6)	104,646 (43.0)	52,381 (21.5)	21,015 (8.6)	22,245 (9.1)	9,905 (4.1)	115,216 (47.4)
Dementia	88,363	5 (<0.1)	102 (0.1)	2,294 (2.6)	10,578 (12.0)	36,488 (41.3)	38,896 (44.0)	51,586 (58.4)

Table 2 Segmented regression analysis for antibiotic prescribing measures (April 2013 - February 2017), age and sex-standardised rates for GP practice consultations rated per million person-months (April 2010 - December 2016), and age and sex-standardised rates for emergency hospital admissions per million population in England (April 2010 – September 2017)

Outcome	Constant	Pre-intervention trend (p)	Change in level (p)	Post-intervention trend (p)	Absolute change in outcome per month during post-intervention period (95% CI)	Relative change by the end of the study (%) (95% CI)
Primary care (CPRD)						
All infections	98.749	0.425 (<0.01)	-3.623 (0.64)	0.327 (0.86)	-5.68 (-23.23, 11.86)	-4.3 (-17.5,8.9)
Community acquired pneumonia	38.676	-0.099 (<0.01)	1.011 (0.68)	0.031 (0.46)	3.74 (-1.69,9.17)	12.2 (-6.5,30.9)
Mastoiditis	17.149	-0.092 (<0.01)	0.172 (0.93)	0.157 (0.09)	5.39 (0.88,9.92)	55.4 (-6.0,116.8)
Quinsy	8.581	0.000 (0.99)	-0.726 (0.55)	-0.028 (0.75)	-1.31 (-4.02,1.39)	-15.3 (-45.2,14.6)
Meningitis/brain	0.833	-0.003	-0.002	0.024	0.57	96.9

abscess		(0.44)	(0.99)	(0.15)	(-0.01,1.15)	(-53.5,247.5)
Empyema	0.689	0.006 (0.17)	-0.320 (0.29)	-0.027 (0.12)	**-1.01 (-1.66, -0.36)**	**-86.8 (-127.6, -46.1)**
Scarlet fever	11.919	0.379 (<0.01)	-1.687 (0.71)	-0.083 (0.16)	**-11.38 (-21.62, -1.14)**	**-26.7 (-48.6, -4.8)**
Pyelonephritis	21.205	0.206 (<0.01)	-1.466 (0.63)	0.239 (0.88)	-0.78 (-7.59,6.03)	-2.1 (-20.2,16.2)
Secondary care (HES)						
All infections	814.009	3.988 (<0.01)	-10.362 (0.61)	4.639 (0.55)	8.51 (-43.76,60.77)	0.7 (-3.9,5.4)
Community acquired pneumonia	212.169	1.315 (<0.01)	9.739 (0.54)	0.124 (0.19)	-24.80 (-67.81,18.21)	-7.5 (-20.9,5.8)
Hospital acquired pneumonia	19.354	0.329 (<0.01)	-0.013 (0.99)	0.175 (0.06)	**-4.49 (-8.36,-0.62)**	**-9.2 (-17.1,-1.3)**
Mastoiditis	1.005	0.001 (0.44)	0.155 (0.13)	0.006 (0.41)	0.29 (0.00,0.55)	25.4 (-2.4,53.2)
Quinsy	9.600	0.046 (<0.01)	-0.388 (0.19)	0.098 (<0.01)	**1.13 (0.41,1.86)**	**8.3 (2.7,13.9)**
Meningitis	2.721	0.004 (0.10)	0.191 (0.20)	-0.014 (0.02)	-0.33 (-0.71,0.04)	-10.8 (-22.4,0.8)
Brain abscess	0.623	0.001 (0.24)	-0.028 (0.62)	0.000 (0.63)	-0.07 (-0.20,0.07)	-9.3 (-27.3,8.6)

Empyema	1.813	0.001 (0.42)	0.103 (0.32)	0.001 (0.92)	0.09 (-0.17,0.34)	4.5 (-9.1,18.2)
Scarlet fever	0.496	0.016 (<0.01)	0.198 (0.20)	-0.009 (<0.01)	**-0.53 (-0.92,-0.14)**	**-28.0 (-45.6,-10.5)**
Rheumatic fever	0.055	0.0002 (0.35)	0.025 (0.11)	-0.001 (0.23)	-0.003 (-0.04,0.04)	-3.5 (-53.0,46.0)
Pyelonephritis	25.170	0.243 (<0.01)	1.188 (0.19)	0.006 (<0.01)	-5.68 (-8.01,-3.36)	-12.2 (-16.9,-7.4)
Complicated intra-abdominal conditions	56.310	0.094 (<0.01)	0.038 (0.96)	0.164 (0.12)	2.05 (-0.09,4.20)	3.2 (-0.3,6.7)
Complicated skin and skin structure conditions	203.003	0.322 (<0.01)	2.398 (0.58)	0.469 (0.56)	6.65 (-5.35,18.65)	2.9 (-2.8,8.5)
Complicated urinary tract conditions	248.265	0.928 (<0.01)	0.830 (0.89)	-1.654 (<0.01)	**-74.07 (-109.11,-39.03)**	**-22.4 (-32.3,-12.5)**
Sepsis	35.956	0.542 (0.19)	-10.231 (0.44)	4.735 (<0.01)	111.36 (54.83,167.88)	132.2 (-14.0,278.4)
Controls (excluding admissions with a mention of condition)						
Diabetes	50.155	-0.019 (0.17)	1.707 (0.04)	0.021 (0.92)	**2.87 (0.76,4.98)**	**5.9 (1.3,10.5)**
Dementia	18.639	-0.041 (<0.01)	0.935 (0.22)	-0.142 (0.02)	**-1.99 (-3.97,-0.01)**	**-13.3 (-26.0,-0.5)**

Figure 1 Segmented regression analysis for age and sex-standardised general practitioner consultation rates per million person-months for all conditions combined. The solid line is for the estimates of the segmented regression model; the dotted line is for the estimated without intervention. Implementation of the Quality Premium (represented by a vertical grey line) occurred in April 2015

Figure 2 Segmented regression analysis for age and sex-standardised emergency hospital admission rates per million population for all conditions combined. The solid line is for the estimates of the segmented regression model; the dotted line is for the estimated without intervention. Implementation of the Quality Premium (represented by a vertical grey line) occurred in April 2015

Figure 3 Segmented regression analysis for age and sex-standardised emergency hospital admission rates per million population for the community and hospital-acquired pneumonia. The solid line is for the estimates of the segmented regression model; the dotted line is for the estimated without intervention. Implementation of the Quality Premium (represented by a vertical grey line) occurred in April 2015

Figure 4 Segmented regression analysis for age and sex-standardised emergency hospital admission rates per million population for quinsy and scarlet fever. The solid line is for the estimates of the segmented regression model; the dotted line is for the estimated without intervention. Implementation of the Quality Premium (represented by a vertical grey line) occurred in April 2015

Figure 5 Segmented regression analysis for age and sex-standardised emergency hospital admission rates per million population for sepsis. The solid line is for the estimates of the segmented regression model; the dotted line is for the estimated without intervention. Implementation of the Quality Premium (represented by a vertical grey line) occurred in April 2015

Figure 1

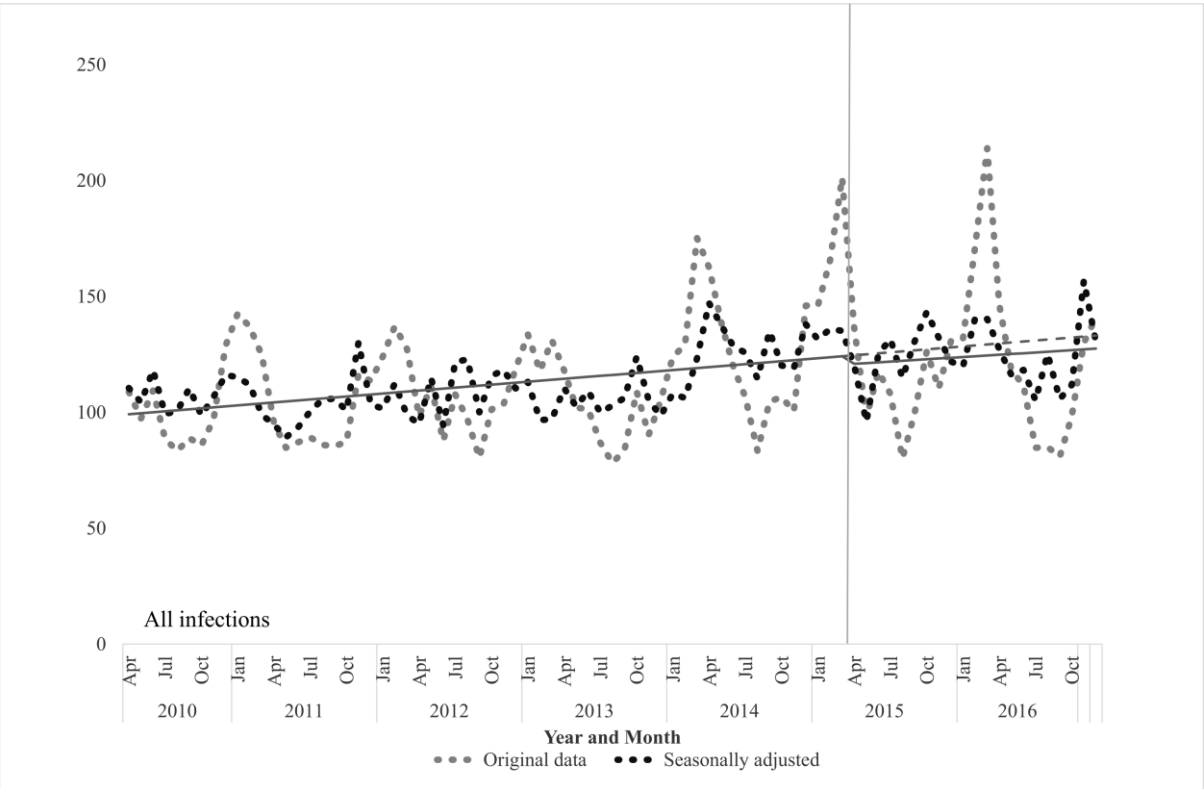

Figure 2

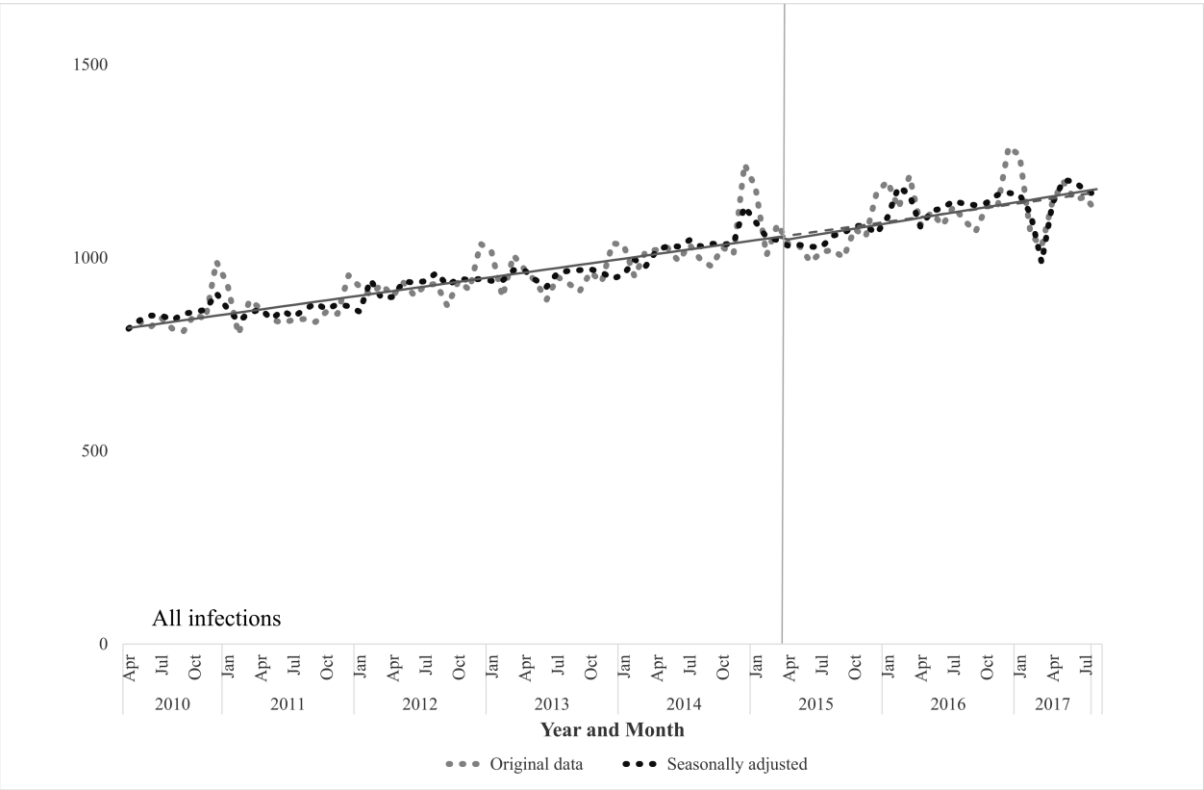

Figure 3

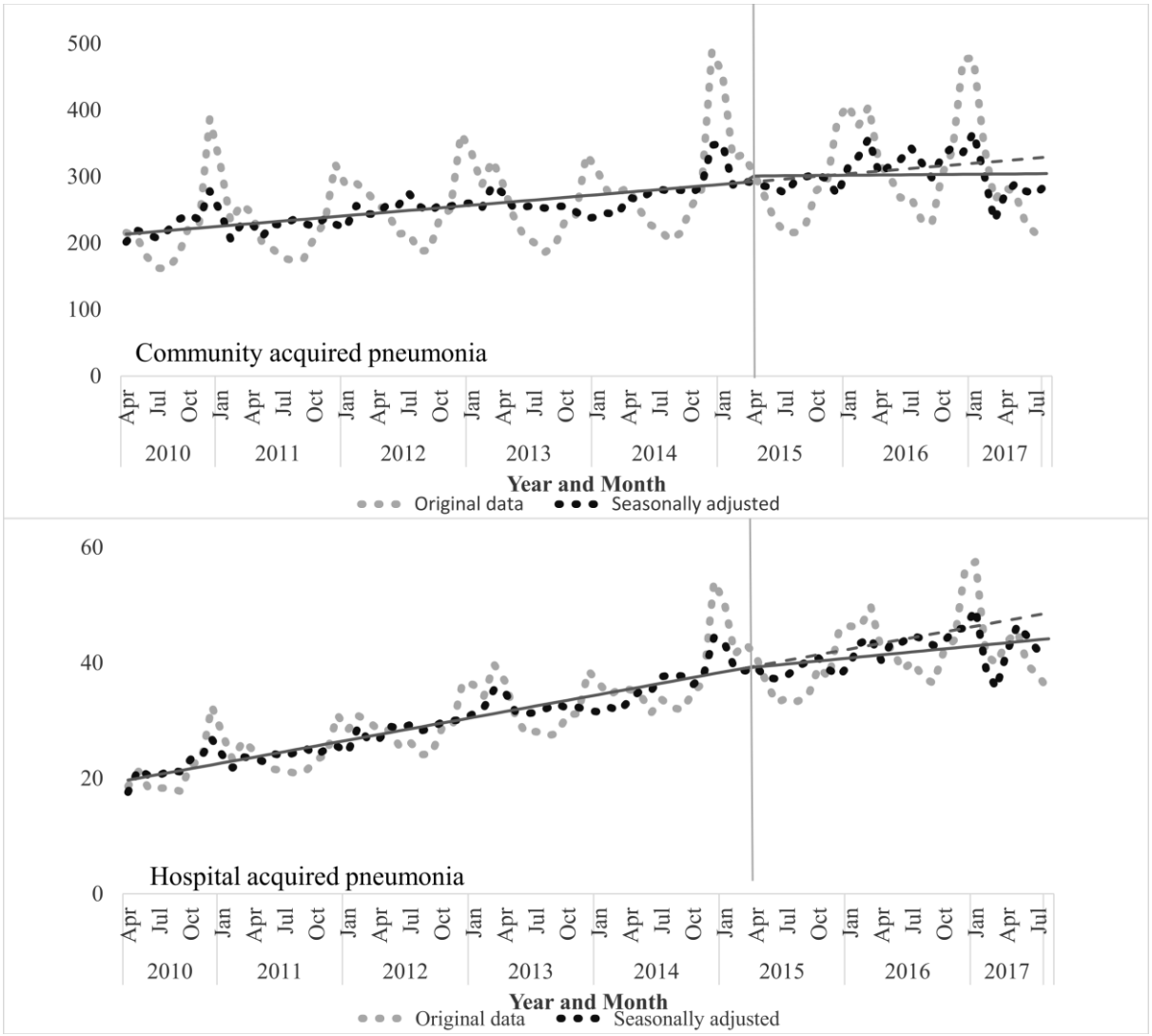

Figure 4

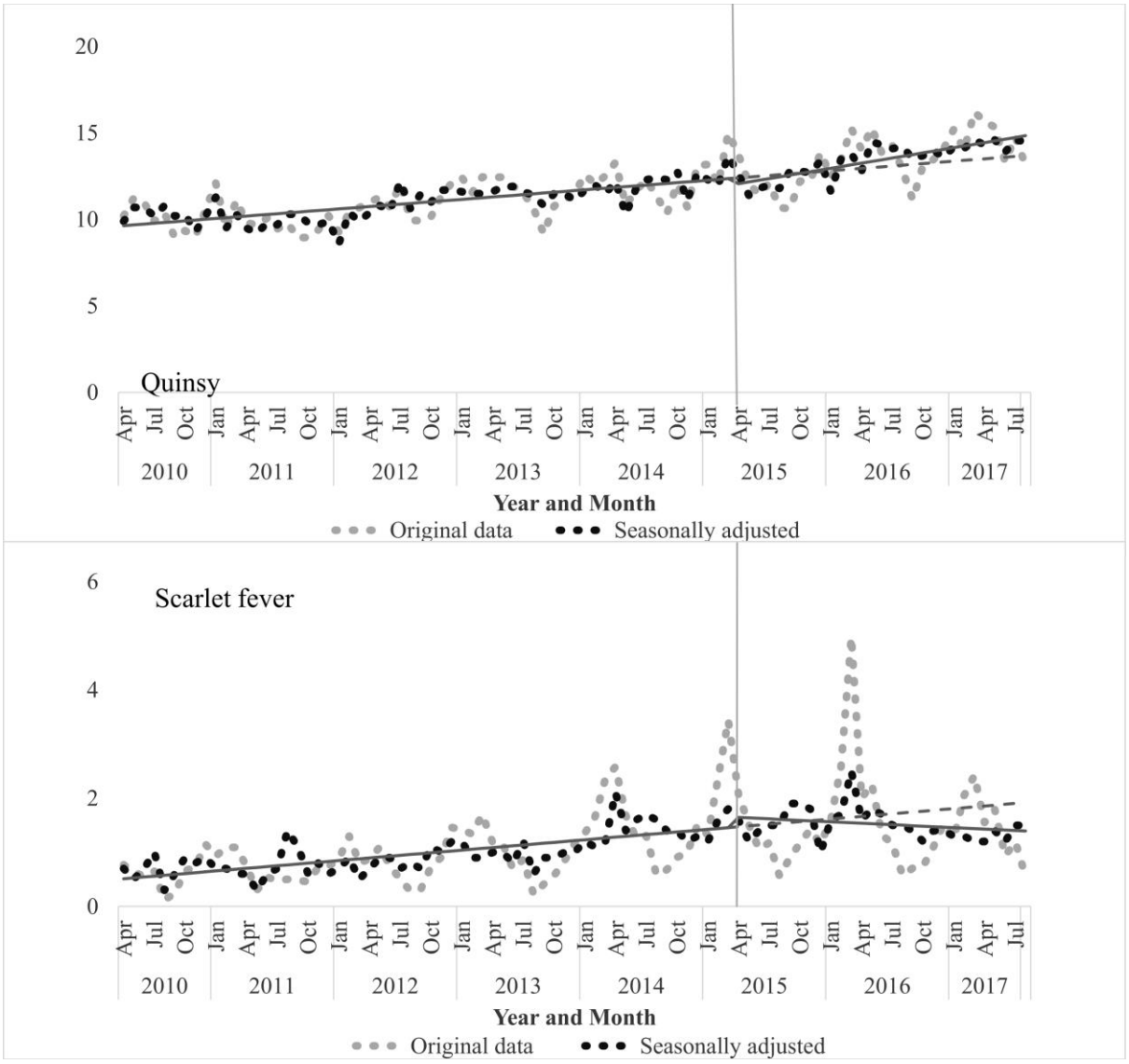

Figure 5