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Complete List of Authors:	Llewelyn, Martin; Brighton and Sussex Medical School, Global Health and Infection; University Hospitals Sussex NHS Foundation Trust, Microbiology and Infection Grozeva, Detelina; Cardiff University, Centre for Trials Research Howard, Philip; Leeds Teaching Hospitals NHS Trust, Pharmacy; University of Leeds, School of Healthcare Euden, Joanne; Cardiff University, Centre for Trials Research Gerver, Sarah; Public Health England, Division of Healthcare-Associated Infection and Antimicrobial Resistance Hope, Russell; Public Health England Colindale, HCAI & AMR; Heginbothom, Margaret ; Public Health Wales, Healthcare Associated Infection, Powell, Neil; Royal Cornwall Hospital Trust, pharmacy department Richman, Colin; Rx-info Limited Shaw, Dominick; University of Nottingham, NIHR Respiratory Biomedical Research Centre Thomas-Jones, Emma; Cardiff University, Centre for Trials Research West, Robert; University of Leeds, Leeds Institute of Health Sciences Carrol, Enitan; University of Liverpool Institute of Infection and Global Health, Department of Clinical Infection, Microbiology and Immunology Pallmann, Philip; Cardiff University Sandoe, Jonathan; Leeds Teaching Hospitals NHS trust, University of Leeds, Microbiology
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Impact of introducing procalcitonin testing on antibiotic usage in acute NHS hospitals during the first wave of COVID-19 in the UK: a controlled interrupted time series analysis of organisation-level data

Martin J LLEWELYN[1]*†, Detelina GROZEVA[2]†, Philip HOWARD[3], Joanne EUDEN[2], Sarah M GERVER[4], Russell HOPE[4], Margaret HEGINBOTHOM[5], Neil POWELL[6], Colin RICHMAN[7], Dominick SHAW[8], Emma THOMAS-JONES[2], Robert M WEST[9], Enitan D CARROL[10], Philip PALLMANN[2]‡, Jonathan A T SANDOE[11]‡ on behalf of the PEACH study team**

Running Title: Impact of procalcitonin on antibiotic use during COVID-19.

[1] Global Health and Infectious Diseases, Brighton and Sussex Medical School, University of Sussex, Brighton, BN1 9PS, UK

[2] Centre for Trials Research, Cardiff University, Neuadd Meirionnydd, Heath Park, Cardiff, CF14 4YS, UK

[3] School of Healthcare, University of Leeds, Leeds, LS2 9JT, UK and Pharmacy, Leeds Teaching Hospitals, Leeds, LS1 3EX, UK

[4] Division of Healthcare Associated Infections and Antimicrobial Resistance, National Infection Service, Public Health England, 61 Colindale Avenue, London, NW9 5EQ, UK

[5] Healthcare Associated Infection, Antimicrobial Resistance and Prescribing Programme, Public Health Wales, 2 Capital Quarter, Tyndall St, Cardiff, CF10 4BZ, UK

[6] Pharmacy Department, Royal Cornwall Hospital Trust, Truro, Cornwall, TR1 3LJ, UK

[7] Rx-Info Ltd, Exeter Science Park, 6 Babbage Way, Exeter, EX5 2FN, UK

[8] NIHR Respiratory Biomedical Research Centre, University of Nottingham, Nottingham, NG5 1PB, UK

[9] University of Leeds, Worsley Building, Clarendon Way, Leeds, LS2 9LU, UK

[10] Department of Clinical Infection, Microbiology and Immunology, University of Liverpool Institute of Infection, Veterinary and Ecological Sciences, Ronald Ross Building, 8 West Derby Street, Liverpool, L69 7BE, UK

[11] Department of Microbiology, The Old Medical School, The General Infirmary at Leeds, Leeds, LS1 3EX, UK

* Corresponding author: email M.J.Llewelyn@bsms.ac.uk

† Equal contribution.

‡ Equal contribution.

** Members are listed in the Acknowledgements section.

Summary

Background

Blood biomarkers have the potential to help identify COVID-19 patients with bacterial coinfection in whom antibiotics are indicated. During the COVID-19 pandemic, procalcitonin testing was widely introduced at hospitals in the United Kingdom to guide antibiotic prescribing. We have determined the impact of this on hospital-level antibiotic consumption.

Methods

We conducted a retrospective, controlled, interrupted time series analysis of organisation-level data describing antibiotic dispensing, hospital activity and procalcitonin testing for acute hospitals/hospital Trusts in England and Wales during the first wave of COVID-19 (24th February to 5th July 2020).

Findings

In the main analysis of 105 hospitals in England introduction of procalcitonin testing in the Emergency Department / Acute Medical Admission Unit was associated with a statistically significant decrease in total antibiotic use of -1.08 (95%CI: -1.81;-0.36) Defined Daily Doses (DDDs) of antibiotic/ admission/ week/ Trust. This effect was then lost at a rate of 0.05 (95%CI: 0.02;0.08) DDDs/ admission/ week. Similar results were found specifically for first-line antibiotics for community acquired pneumonia and for COVID-admissions rather than all admissions. Introduction of procalcitonin in the Intensive Care setting was not associated with any significant change in antibiotic use.

Interpretation

At hospitals where procalcitonin testing was introduced in Emergency Departments / Acute Medical Units this was associated with an initial, but unsustained, reduction in antibiotic use. Further research should establish the patient-level impact of procalcitonin testing in this population and understand its potential for clinical effectiveness.

Introduction

Identifying COVID-19 patients who have bacterial co-infection and who would benefit from antibiotic treatment is clinically challenging. Measurement of blood biomarkers of bacterial infection could help reduce unnecessary antibiotic prescribing. Biomarkers, such as C-reactive protein (CRP) and neutrophil count, are often elevated in patients with COVID-19.[1] This, and experience of previous influenza pandemics, during which bacterial co-infection was common,[2] has driven considerable, unnecessary antibiotic use in COVID-19 patients. In the UK, during the first wave of the pandemic, 83.1% of hospitalised patients received empiric antibiotic treatment.[3] It is now established that bacterial co-infection is very uncommon in acute COVID-19.[4-7] Overall volumes of antibacterial use at the beginning of the COVID-19 pandemic decreased in both primary and secondary settings, although antibacterial usage in hospital admissions increased steeply in April 2020. Use of antibacterials prescribed for respiratory infections and broad-spectrum antibacterials increased in both settings.[8] Patients who have prolonged hospital stays, however, frequently culture antibiotic resistant nosocomial Gram-negative pathogens[9] highlighting that early inappropriate antibiotic treatment of COVID-19 may impact on both individual patients and the wider selection of antimicrobial resistance.

Procalcitonin (PCT) is an inflammatory biomarker that rises in bacterial infection and falls in response to antibiotic treatment with greater sensitivity and specificity for bacterial infection than CRP.[10, 11] It is approved by the United States (US) Federal Drugs Administration (FDA) to support antibiotic decision making in lower respiratory tract infection and in sepsis.[12] Nevertheless, current US and United Kingdom (UK) national guidelines on management of community acquired pneumonia (CAP) recommend against the use of PCT to guide antibiotic prescribing.[13, 14]

Early in the COVID-19 pandemic, studies reported that while substantial elevation of PCT (>0.5 ng/mL) is a feature of severe COVID-19, associated with increased mortality risk, levels in most patients are low in acute disease.[15] During the first pandemic wave in the UK, many National Health Service (NHS) hospitals introduced PCT testing to guide antibiotic decision making, particularly in emergency

departments and acute medical units (EDs/AMUs).[16] Between March and July 2020 PCT use increased from 48% to 84% of critical care units and from 11% to 51% of EDs/AMUs[16]. This was despite COVID-19-specific guidance from the National Institute for Health and Care Excellence (NICE) that PCT testing should not be used routinely in this setting.[17]

The Procalcitonin Evaluation of Antibiotic use in COVID-19 Hospitalised patients (PEACH) Study[18] is evaluating whether the use of PCT testing to guide antibiotic prescribing safely reduced antibiotic use among patients admitted to acute UK NHS hospitals with COVID-19.

Here we report the impact of PCT testing on organisation-level (i.e. NHS Trusts/hospitals) antibiotic use for the treatment of patients in England and Wales during the first wave of the pandemic.

Methods

Approvals

Research approval for the PEACH study was provided by Health Research Authority (HRA) and Health and Care Research Wales (HCRW). Ethics approval was provided by West Midlands - Solihull Research Ethics Committee (REC Reference 21/WM/0052).

Study design and setting

This was a retrospective controlled interrupted time-series analysis of aggregated, organisation-level data. We sought to quantify the organisation-level impact of introducing PCT testing on antibiotic usage during the first wave of the COVID-19 pandemic in English and Welsh hospitals, defined for the purposes of this study as ISO weeks 9 to 27 of 2020 (24th February to 5th July).[16] The study was designed and reported according to STROBE guidelines[19] and additional reporting considerations specific to interrupted time series.[20]

Trusts/hospitals were categorised either as "Always Users" if PCT testing was in use prior to the first wave of COVID-19 and continued to use during the first wave either in the ICU or ED/AMU or both, "Never Users" if PCT testing was neither used before nor introduced during the first wave, or "PCT Adopters" if PCT testing was introduced or expanded during the first wave, either in the ICU setting or among ED/AMU admissions or both.

Variables, measures and data sources

Weekly antibiotic dispensing data for each acute NHS Trust in England and hospital in Wales were provided by Rx-Info Ltd (https://www.rx-info.co.uk/). NHS Trusts were one or more hospitals under the same management. These data comprised total defined daily doses (DDDs) per week per NHS Trust or hospital of all types of antibiotics dispensed to hospital locations (excluding antimycobacterial agents). DDD data were also compiled for a pre-specified subgroup of antibiotics that are used to treat

CAP: amoxicillin (IV or oral), ceftriaxone (IV), cefuroxime (IV), clarithromycin (IV or oral), co-amoxiclav (IV or oral), doxycycline (oral), erythromycin (oral) and levofloxacin (IV or oral).[17, 21]

Weekly hospital activity data were provided by PHE and Public Health Wales (PHW). These included total admissions, total occupied overnight bed days, COVID-positive admissions and COVID-positive bed days per week per NHS Trust (England) or hospital (Wales). A COVID-positive admission was defined as patients with a positive SARS-CoV PCR test <14 days pre-admission or at any time during their hospital stay. Data for hospital activity in England were extracted from PHE's source of the Secondary Use Service on 15th December 2020.[22] Data for hospital activity recorded in patient administration systems in NHS hospitals in Wales were extracted from the Clinical Surveillance software system ICNET on 8th January 2021.

PCT usage data were gathered through a web-based survey as described previously.[16]. For the Trusts/hospitals introducing PCT testing, their first week of PCT use was defined as the ISO week following the reported introduction date.

Bias

We attempted to collect data from all acute NHS Trusts/hospitals in England and Wales to reduce the risk of bias. Where data were excluded, we report the reason for the exclusion. Antibiotic usage data, hospital activity data and PCT usage data were collected by separate team members and data were analysed by a team who were not involved in data collection. Data collection and analysis were pre-specified in a statistical analysis plan which can be found in the Supplementary material.

Study size

The study size was determined by the number of acute NHS Trusts/hospitals in England and Wales. To provide an indication of the power of this study, the following scenario was explored: there are 25 Trusts who always use, 25 who never use, and 50 who adopt PCT testing, 18 weeks of observations during the first wave, adopters implement testing after 9 weeks on average, there is an intra-class correlation coefficient of 0.6 relating to weekly measurements within Trusts. This would yield 100

times 18 observations, giving 900 with, and 900 without, PCT testing. After adjusting for clustering, this is an effective sample size of 80 plus 80 and therefore a standardised effect size of 0.45, that is a medium effect size, might be estimated with 80% power. The power calculation was done in R using the function power.t.test based on a formula established by Donner *et al.*[23]

Outcomes

The primary study outcome was total antibiotic DDDs per admission per week per NHS Trust/hospital.

Secondary outcomes were: first-line CAP antibiotic DDDs (defined as above) and individual antibiotic DDDs per admission per week, and total antibiotic DDDs and CAP antibiotic DDDs per occupied overnight bed days per week per NHS Trust/hospital.

Quantitative variables and statistical analysis

The three datasets (antibiotic usage, hospital activity and PCT usage) were merged to create a single analysis dataset by matching the NHS Organisational Data Service (ODS) Trust/hospital codes in the respective datasets. We anticipated that the analysis might be confounded by changes in antibiotic prescribing over time as well as changes in the number of COVID-19 admissions over time, the introduction of NICE guidance NG173[17] and the size of Trusts/hospitals so these were all included either in the primary model or sensitivity analyses.

English and Welsh data were analysed separately because of differences in the way the NHS is organised in these countries and resulting structural differences in the data. For example, the unit of data collection in England was the NHS Trust (typically comprising multiple hospitals) whereas for Wales data were available for individual hospitals.

Main analysis

A controlled interrupted time-series (cITS) analysis was undertaken to estimate the organisation-level effects of introducing PCT on the usage of antibiotics (normalised by Trust/hospital activity), taking into account underlying trends and other covariates. To account for nonlinearity of trend over time, a

generalised additive mixed model (GAMM)[24] was fitted to the data with NHS Trust/hospital as a random-effect variable, allowing for variable dates of introduction of PCT testing across the Trusts/hospitals.[25, 26] The GAMM included a cubic spline smoothing function as a fixed effect for time, separate fixed effects for use of PCT testing (coded 0 for no use and 1 for use in a particular week) in the ICU and ED/AMU, respectively, and their respective linear interactions with week, to assess level and/or trend changes (relative to the overall nonlinear trend) in the outcome following the introduction of PCT testing. COVID-positive admissions as a percentage of total admissions per week per Trust/hospital was included as a fixed-effect covariate. Random Trust/hospital-level intercepts and slopes were included in the model to capture the variability between Trusts/hospitals. The effective degrees of freedom for the smooth term were 8.8, while the number of knots used in the model was 9. Both were selected based on the default recommended by the R package 'mgcv'. The model was checked for autocorrelation and moving averages by assessing autocorrelation and partial autocorrelation function plots by using the R package 'forecast'.[27]

Additional and sensitivity analyses

Instead of modelling trend changes with interaction terms between PCT use and week, we added step effects at 4 and 8 weeks after PCT was introduced in the corresponding Trusts/hospitals, to assess if any step change effect immediately following the introduction of PCT diminished in a nonlinear way.

To assess if the organisation size had an effect on antibiotic use we included as a measure of Trust size the publicly available 2019/20 Estates Return Information Collection (ERIC) data (data download: 18th May 2021, https://digital.nhs.uk/data-and-information/publications/statistical/estates-returns-information-collection).

To assess whether the introduction of NICE rapid COVID-19 guidance NG173 [17] on 1st May 2020 led to a level and/or trend change in the outcome we included a fixed effect and interaction term with week using a binary dummy variable (0 before and 1 after the introduction date) for all Trusts.

All analyses were performed in R version 4.1.0, with add-on packages 'mgcv' for GAMMs, 'forecast' for autocorrelation functions and 'ggplot2' for graphics. The statistical significance level was set to double-sided 5%.[28]

Missing data

NHS Trusts/hospitals which did not provide information about their PCT usage were excluded (**Figure 1**). Where activity or antibiotic data were missing for a Trust/hospital, these Trusts/hospitals were excluded (**Figure 1**). The percentage of missing data is reported for all variables (DDDs and activity data) separately for the English and Welsh data (**Table S1).**

In addition, activity data for a total of five weeks for three Trusts were excluded because these individual data points were outliers.

Role of the funding source

The funder of the study had no role in the design, data collection, analysis, interpretation or writing of this report. The corresponding author had full access to all the data and final responsibility for the decision to submit for publication.

Results

Of 151 acute Trusts/hospitals in England and Wales, 148 responded to the survey of PCT use[16]. Twenty-seven were excluded from the analysis because of missing data either on date of PCT introduction, antibiotic use or hospital activity, thus leaving 121 (80%) for the final analysis (**Figure 1**). Based on PCT use these included: 35 "Always Users" (one in Wales), 19 "Never Users" (none in Wales) and 67 "PCT Adopters" (15 in Wales). Thirty-eight NHS Trusts/hospitals started using PCT in an ICU setting during the studied period, while 33 started using PCT in ED/AMU (**Figure S5**). The mean and median of the elapsed weeks from the start of the studied period (24th Feb 2020) until the introduction of the PCT for the Trusts which introduced PCT was 7.8 and 7 weeks, respectively (range: 1-18 weeks).

The variables of primary interest (DDDs per week per Trust/hospital, number of admissions per week per Trust/hospital, number of occupied overnight bed days per week per Trust/hospital) had no missing values, while the variable for COVID-positive admissions had 4.4% missing data (**Table S1**).

Descriptive statistics for antibiotic consumption and hospital activity data are shown in **Table 1** and broken down by category of PCT usage in **Table S2**. Overall use of antibiotics varied 150-fold (from 188 to 28,207 DDDs per week) across different Trusts and approximately 15-fold when normalised by admissions or bed days. English NHS Trusts used a median of 5.9 (range: 1.7-31.3) antibiotic DDDs per admission per week, or 2.3 antibiotic DDDs per occupied overnight bed day (range: 0.5-7.3) (**Table 1, Figure S2**). There was also marked variation in antibiotic use over the course of the first wave of the COVID-19 pandemic, starting in late February / early March and peaking in late April (**Figure 2, Figures S1-S5**) reflecting the time-course of hospital activity over the pandemic.

Hospitals in Wales prescribed more DDDs per admitted patient per week (median 8.9, range: 1.9-49.9) but slightly fewer per occupied overnight bed day per week per hospital (median 1.6, range: 0.2-13.4) (**Table 1, Figure S4**). In view of the small number of studied hospitals in Wales, and that all but one adopted PCT during the pandemic, the main analyses of the impact of PCT testing were restricted to the 105 Trusts in England.

Impact of PCT use on antibiotic consumption

The time-course of changes in antibiotic use at NHS Trusts during the first wave of the pandemic modelled by the nonlinear smooth term of the GAMM according to PCT is shown in **Figure 3A.** The results of the cITS analysis are presented in **Table 2**. There was no statistically significant change in the level or trend of DDDs per admission per week after PCT introduction in the ICU (p=0.21). There was, however, a statistically significant decrease (p=0.003) by -1.08 (95% CI: -1.81; -0.36) DDDs per admission per week per Trust immediately following the introduction of PCT in the ED/AMU, followed by a statistically significant (p=0.004) increase in antibiotic prescribing of 0.05 (95% CI: 0.02; 0.08) DDDs per admission per week. The variability due to Trust (**Figure 3B**) corresponded to an ICC of 0.61.

The effect of the percentage of COVID-positive admissions per total admissions each week was also highly significant (p<0.001), DDDs per admission increasing by 0.32 (95% CI: 0.29; 0.34) with each 1% increase in COVID-positive admissions, which ranged between 0 and 5% for most Trusts in most weeks (**Figure S1**).

Sensitivity analyses

To determine whether the introduction of NICE rapid guidance NG173 in ISO week 19, which recommended against use of PCT to guide antibiotic prescribing, had an effect we assessed the impact of a fixed-effect and an interaction term in the model at ISO week 19. This resulted in nearly identical estimates for both level of DDDs per admission (-1.09, 95% CI: -1.81; -0.38, p=0.003) and trend changes of DDDs per admission (0.05, 95% CI: 0.02; 0.08, p=0.003) after introduction of PCT testing in ED/AMU **(Table S3).**

To assess the potential for nonlinear increases after the initial drop in DDDs per admission following the introduction of PCT we replaced the interaction effects between PCT introduction and week with additional step change effects at 4 and 8 week. This made the estimated effect sizes smaller than in the primary model and no longer statistically significant (**Table S4**).

When assessing impact of Trust size by adding the ERIC categories in the model, estimates of level and trend changes following PCT introduction were nearly unchanged, and there were no statistically significant differences between ERIC categories (**Table S5**).

As part of additional sensitivity checks, the main analysis model was run with log-transformed outcome variable and added ARMA(2,1) term (as determined by applying the R package 'forecast'), respectively. The two models produced similar results to the main model (Tables S6 and S7).

Secondary outcome analyses

When repeating the main analysis but using DDDs per occupied overnight bed days per week per Trust, rather than per admission, the level and trend changes following PCT introduction in the ED/AMU were smaller than those found in the model of DDDs normalised by admissions and were not statistically significant (**Table S8**).

Repeating the main analysis for specifically CAP antibiotics **(Tables S9 and S10)** again identified a statistically significant level reduction in antibiotic use followed by an upward trend when use was normalised by admissions but no statistically significant change was identified when expressed per occupied overnight bed days.

Discussion

The PCT use in 105 NHS Trusts was studied for the period of the first COVID-19 wave in England (24th February to 5th July 2020). Of the 105 Trusts, 34 were using PCT testing already, 19 did not introduce it in the studied period and 52 adopted PCT use in either ICU or ED/AMU setting or in both. Using aggregated data on antibiotic use, clinical activity and PCT testing from the great majority (80%) of acute Trusts in the English NHS we have demonstrated that hospitals which introduced PCT testing in ED/AMU during the first wave of the COVID-19 pandemic experienced a drop in overall antibiotic use of approximately 1 DDD of antibiotic per admission per week. Or expressed in another way, a Trust admitting 100 patients in a week would have seen a reduction of 100 DDD in the week after introducing PCT, compared to a Trust that did not introduce PCT. This reduction was then gradually eroded over time such that, on average, it would be expected that the effect would be lost after about 20 weeks. We found a similar impact looking just at antibiotic agents which are first-line treatments for CAP, and normalising for COVID admissions rather than all admissions.

Interestingly, we found no impact of introducing PCT in ICU. This may reflect high existing levels of antimicrobial stewardship and close working relationships between intensivists and infection specialists, which may lessen the impact of PCT testing. The analysed DDDs and hospital activity data were overall data per NHS Trust/hospital and not broken down for ED/AMU or ICU. This could explain why there was no effect observed in an ICU setting.

Quantifying antibiotic use per occupied overnight bed day rather than per admission produced slightly smaller point estimates for change in level and trend as in the primary analysis but these differences were not statistically significant. This can be explained by the greater variability between Trusts/hospitals in bed days than in admissions. It may also be explained by clinicians using PCT to guide decisions early in a patient's COVID admission combined with most antibiotic prescribing being initiated early in the course of the disease. When the whole of a patient's stay is considered, as in the bed day analysis, the impact of PCT testing is diluted. Confirming this would require patient-level

prescribing data linked to PCT testing. However, previous analyses of antibiotic use normalised by admissions or bed days have highlighted the former is more accurate for acute settings with shorter length of stay as in our analysis.[29]

We find that the initial impact of PCT testing was gradually lost over time. Of note, this is an absolute effect, not relative to other Trusts/hospitals and is likely related to sustainability, which is a challenge for any antibiotic stewardship intervention.[30] Our finding likely reflects PCT testing being introduced without supporting aspects of a complex intervention such as a pathway for PCT use, ongoing education, audit and feedback. Again, the retrospective nature of this study means we lacked qualitative data about how PCT testing was introduced, and further research is underway within the PEACH research programme to understand this properly.

The magnitude of variation in antibiotic use we have observed appears very large, but reflects variation both between Trusts/hospitals, variation with respect to case mix (patients with COVID-19 or not) and over the time course of the pandemic. When corrected for clinical activity the magnitude of variation falls by approximately ten-fold and is compatible with previous studies of secondary care antibiotic use across healthcare systems.[31, 32] Andrews *et al*. have recently described a marked overall reduction in secondary care antibiotic use, but a marked increase in antibiotic use per hospital admission compared to seasonal averages during the first wave of the COVID-19 pandemic.[8] Our data for the average and range of antibiotic consumption are entirely consistent with the data they report.

In accordance with our prespecified analysis plan we have included data from NHS hospitals in Wales but excluded these from the main analysis because: 1) data were not directly comparable, being available for hospitals in Wales, but for Trusts in England; 2) it became evident that there were structural differences in services in the two nations that could cause unmeasurable bias (reflected in the higher antibiotic use among Welsh hospitals and longer hospital stays for COVID patients in Wales) 3) PCT was almost universally adopted in Wales meaning a relevant control group was not available. In addition, the natural course of the pandemic progressed differently in Wales than in England with

the number of admissions, number of occupied overnight bed days, number of COVID-19 admissions and occupied overnight bed days per week having different time courses (**Figure S4**).

The most important limitation of our study is its observational and opportunistic nature. PCT testing was introduced widely in the NHS in an uncoordinated and variable way and our data are subject to forms of bias which we cannot control for or fully measure. For example, regression to the mean may explain declines in antibiotic use after PCT testing was introduced. In addition, we lack any patient level data and cannot explore aspects of implementation likely to be important in the impact of PCT (e.g. intervention fidelity). We have used data on drugs dispensed from pharmacy as a surrogate for drugs received by patients and cannot account for any drug wastage or poor compliance, thus this method may overestimate DDD usage. Data were analysed from 80% of English Trusts distributed from across the country and should therefore be representative, but a risk of bias caused by exclusion of some Trusts is possible. Due to the nature of the available aggregated organisation-level data, we were not able to test for potential confounders apart from accounting for Trust size in the model. There were no statistically significant differences between the ERIC categories (Table S4). The current analysis was designed to assess the impact PCT testing on antibiotic consumption at an organisational level. A subsequent patient-level analyses will allow to consider a large number of potential confounders, including many patient-level variables.

Nevertheless, these weaknesses, along with the magnitude of variation, are likely to increase the risk of our study producing a false negative result and failing to detect an impact of PCT use on antibiotic prescribing and so it is most likely we have underestimated the true impact. At -1.08 DDDs per admission per week per Trust, the impact we have detected on the level of antibiotic consumption is small but represents approximately 18% reduction from the national median of 5.9. For comparison, the NHS standard contract requires hospitals to achieve a 1% year-on-year reduction in total antibiotic use.[33] Our data indicate that PCT testing has the potential to be used to reduce antibiotic overuse in COVID-19 patients. Further qualitative work and analysis of patient-level impact are needed to explore our findings further and to seek evidence for clincial effectivenss of PCT testing in this patient group.

Data sharing

Data Availability Statement: Data available on reasonable request from corresponding author.

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PEACH study team:

Mahableswhar Albur, Claire Berry, Stuart E Bond, Lucy Brookes-Howell, Enitan D Carrol, Paul Dark, Joanne Euden, Sarah M Gerver, Thomas P Hellyer, Josie Henley, Russell Hope, Susan Hopkins, Philip Howard, Martin J Llewelyn, Iain J McCullagh, Margaret Ogden, Philip Pallmann, Helena Parsons, David G Partridge, Neil Powell, Colin Richman, Jonathan AT Sandoe, Dominick Shaw, Bethany Shinkins, Tamas Szakmany, Emma Thomas-Jones, Stacy Todd, Robert M West.

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M.J.L., J.E., P.H. are investigators on PRONTO.

P.P., E.C., E.T.J. are investigators on PRONTO, BATCH, PRECISE.

C.R. is company director of RxInfo.

All other authors declare no conflicts of interest.

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Tables

Table 1: Descriptive statistics for the main variables for the 121 NHS Trusts/hospitals in England and Wales. DDDs – defined daily doses of antibiotics; SD – standard deviation

	105 NHS hospital Trusts in England				16 NHS hospitals in Wales			
	Mean	SD	Median	Range	Mean	SD	Median	Range
DDDs per week per Trust/hospital	8,427.3	4408.7	7,489.7	188.1-28,207.3	4,969.0	4,850.6	3,729.9	195.2-54,135.0
Admissions per week per Trust/hospital	1,445.8	869.7	1,224.0	75.0-5,764.0	507.5	331.1	416.0	69-1,702
Occupied overnight bed days per week per Trust/hospital	3,490.7	1,669.4	3,196.0	386.0-11,027.0	2,092.0	1,081.7	2024.0	453-5,306
COVID-positive admissions per week per Trust/hospital	36.0	49.8	17.0	1.0-445.0	11.1	16.8	4.0	0-88.0
COVID-positive occupied overnight bed days per week per Trust/hospital	429.9	474.7	268.0	1.0-3,634.0	126.5	149.0	72.0	0-756.0
DDDs normalised by admissions per week per Trust/hospital	6.6	3.1	5.9	1.7-31.3	10.7	7.0	8.9	1.9-49.9
DDDs normalised by occupied overnight bed days per week per Trust/hospital	2.5	0.8	2.3	0.5-7.3	2.3	1.7	1.6	0.2-13.4

Table 2: Effect sizes estimated by the controlled interrupted time series model of total antibiotic DDDs normalised by admissions per week per Trust (English data). Trend and level changes refer to deviations from the overall trend as modelled by the nonlinear smooth term of the generalised additive mixed model. CI – confidence interval; PCT – procalcitonin; ICU – Intensive Care Unit; ED/AMU – Emergency Department/Acute Medical Unit.

	Estimate	95% CI	P-value
Level change after PCT introduction in ICU	0.38	(-0.21; 0.98)	0.21
Level change after PCT introduction in ED/AMU	-1.08	(-1.81; -0.36)	0.003
Trend change after PCT introduction in ICU	-0.02	(-0.05; 0.01)	0.21
Trend change after PCT introduction in ED/AMU	0.05	(0.02; 0.08)	0.004
% COVID-positive admissions per total admissions	0.32	(0.29; 0.34)	<0.001

Figure 1. Number of NHS Trusts/hospitals included in the analysis classified according to their PCT usage before and during the first wave of the COVID-19 pandemic in the UK

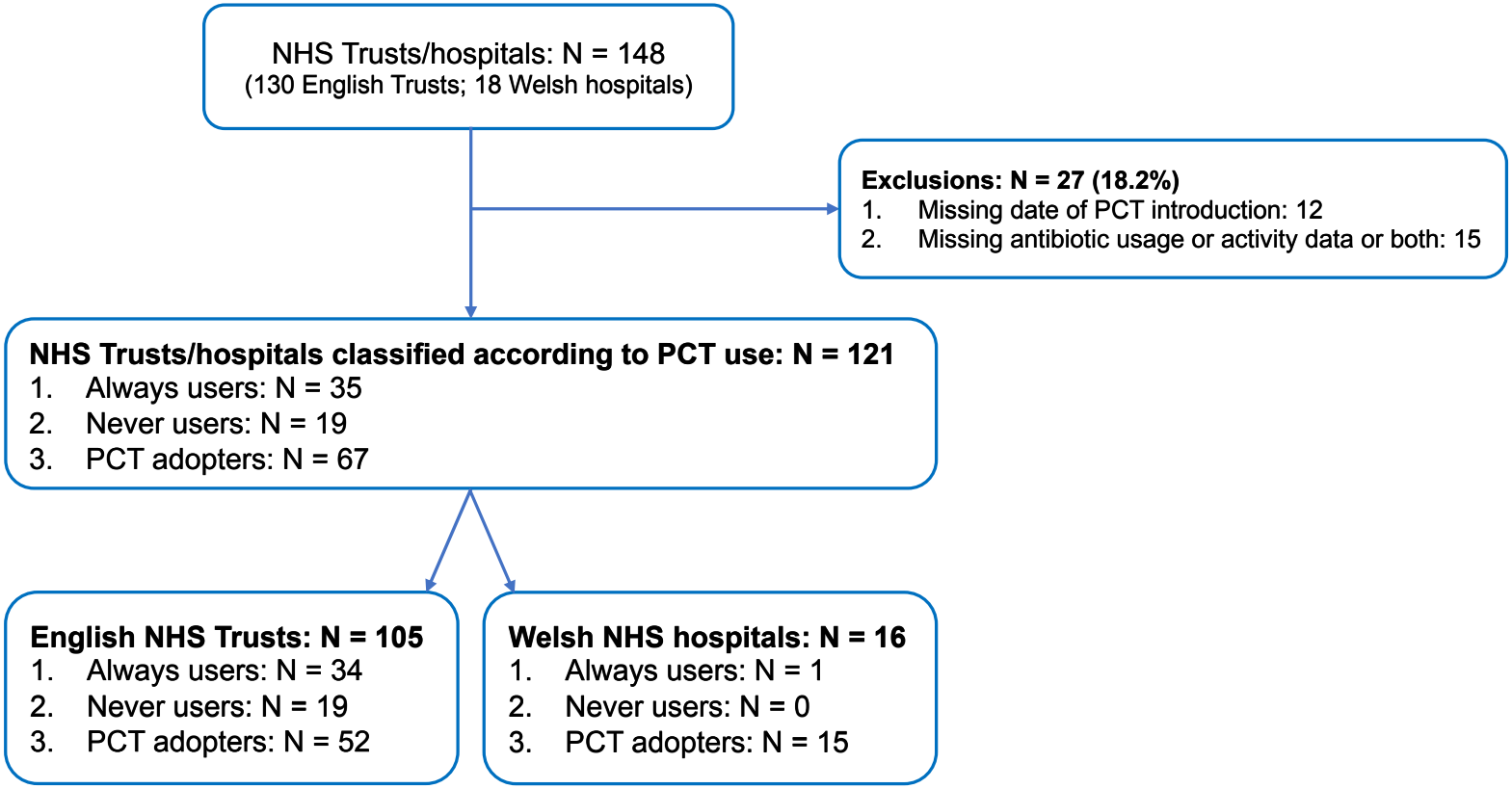
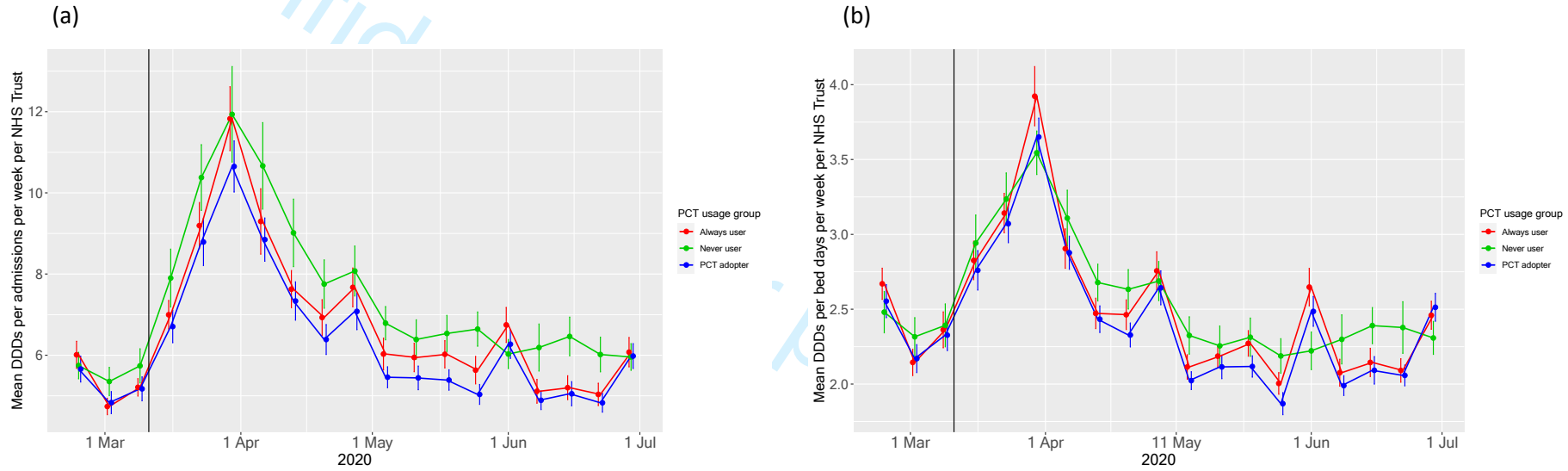


Figure 2. Antibiotic use at 105 NHS Trusts in England during the first wave of the COVID-19 pandemic. Figures show mean antibiotic use per week per NHS Trust by PCT usage

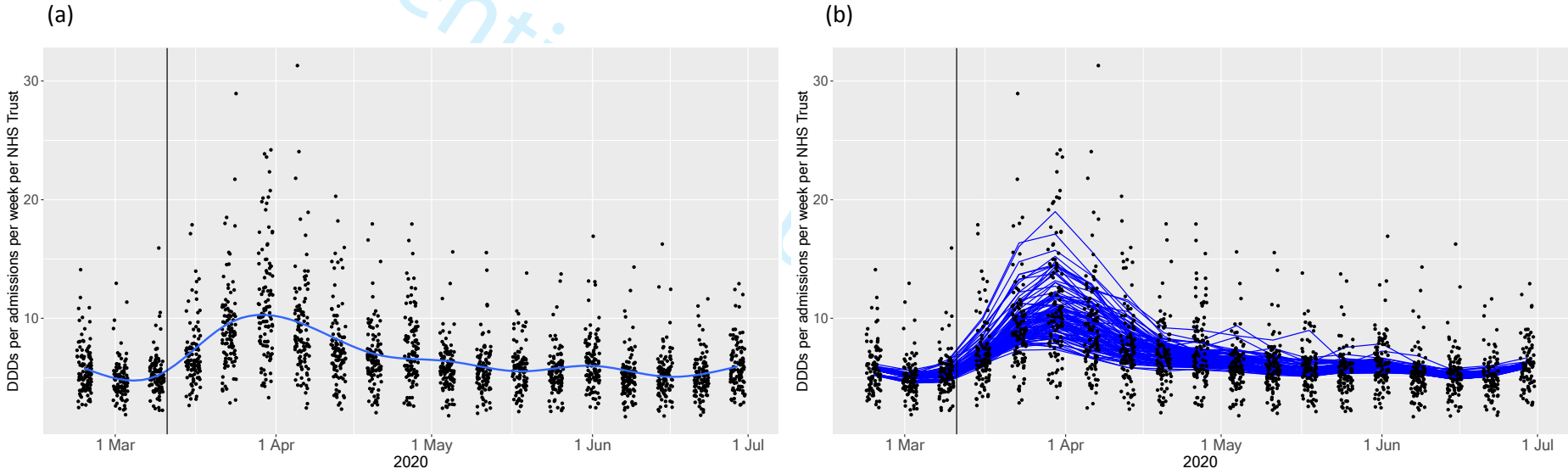
(a) Antibiotic DDDs per admission per week (b) Mean antibiotic DDDs per occupied overnight bed days per week
The error bars in (a) and (b) show the corresponding 95% confidence intervals.



11 Mar 2020: The WHO declares the novel coronavirus outbreak a global pandemic

Figure 3. The time-course changes in antibiotic use at NHS Trusts during the first wave of the COVID-19 pandemic based on the GAMM modelling

(a) Overall time trend for DDDs per admissions per week for the studied time period (24th Feb 2020 – 5th July 2020) based on the model (b) Fitted values for the DDDs per admission per week per NHS Trust based on the model; the blue lines reperesent the separate 105 NHS Trusts (English data)



Supplementary data

Impact of introducing procalcitonin testing on antibiotic usage in acute NHS hospitals during the first wave of COVID-19 in the UK: a controlled interrupted time series analysis of organisation-level data

Llewelyn et al.

The following file is separate in addition to the Supplementary materials:

- Statistical analysis plan file: Llewelyn_et_al_SAP_supplementary_file.pdf

Supplementary Tables and corresponding model equations

Table S1: Missing data (%) for the main variables for all NHS Trusts (English data) or hospitals (Welsh data)

	English data: Missing data (%)	Welsh data: Missing data (%)
DDDs per week per Trust/hospital	0.0	0.0
Admissions per week per Trust/hospital	0.0	0.0
Occupied overnight bed days per week per Trust/hospital	0.0	0.0
COVID-19 admissions per week per Trust/hospital	4.4	25.9
COVID-19 occupied overnight bed days per week per Trust/hospital	1.0	12.0
DDDs normalised by admissions per week per Trust/hospital	0.0	0.0
DDDs normalised by occupied overnight bed days per week per Trust/hospital	0.0	0.0

Table S2: Descriptive statistics for the main variables for all NHS Trusts and for the NHS Trusts classified according to their PCT usage, English data

	All Trusts					Always Users					Never Users					PCT Adopters				
	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max
DDDs per week per Trust	8427.3	4408.7	7489.7	188.1	28207.3	8738.5	4885.7	7250.6	188.1	28207.3	7722.8	3404.6	7762.9	1944.8	23146.6	8482.0	4381.8	7544.7	1280.6	28028.9
Admissions per week per Trust	1445.8	869.7	1224.0	75.0	5764.0	1486.0	1007.6	1182.5	75.0	5764.0	1219.4	715.6	1041.0	193.0	4047.0	1502.6	809.3	1298.5	316.0	4948.0
Occupied overnight bed days per week per Trust	3490.7	1669.4	3196.0	386.0	11027.0	3504.7	1768.7	3029.0	386.0	11027.0	3131.7	1371.0	3134.0	1008.0	6545.0	3613.2	1685.0	3309.5	835.0	10211.0
COVID-19 admissions per week per Trust	36.0	49.8	17.0	1.0	445.0	39.5	56.1	19.0	1.0	445.0	27.6	33.2	14.0	1.0	246.0	36.9	50.4	17.0	1.0	408.0
COVID-19 occupied overnight bed days per week per Trust	429.9	474.7	268.0	1.0	3634.0	455.9	506.0	278.0	1.0	3449.0	357.8	352.9	244.0	1.0	2208.0	439.4	490.3	275.5	1.0	3634.0
DDDs normalised by admissions per week per Trust	6.6	3.1	5.9	1.7	31.3	6.7	3.1	5.8	2.5	31.3	7.4	3.2	6.5	3.2	24.2	6.3	3.1	5.7	1.7	28.9
DDDs normalised by occupied overnight bed days per week per Trust	2.5	0.8	2.3	0.5	7.3	2.5	0.8	2.3	0.5	6.8	2.6	0.7	2.4	1.4	5.5	2.4	0.8	2.3	0.8	7.3

Model equation for the main model. Statistical results are in Table 2 in the article.

$$(DDDs/admissions)_{it} = \beta_0 + f(week)_t + \beta_1 icu_{it} + \beta_2 edamu_{it} + \beta_3 (icu{:}week)_{it} + \beta_4 (edamu{:}week)_{it} + \beta_5 (covid\%)_{it} + u_i + \varepsilon_{it}, \quad \varepsilon \sim N(0, \sigma^2) ,$$

where:

- $(DDDs/admissions)_{it}$ — denotes total DDDs, normalised by admissions for an NHS Trust i during week t
- β_0 — denotes the global intercept, representing the baseline level
- $f(week)_t$ — denotes the nonlinear effect of time (cubic spline)
- β_1 — denotes the effect of PCT testing in ICU on total DDDs, normalised by admissions (i.e., level effect of introduction of PCT testing in ICU)
- icu_{it} — binary covariate denoting if PCT testing was introduced in ICU by week t in NHS Trust i
- β_2 — denotes the effect of PCT testing in ED/AMU on total DDDs, normalised by admissions (i.e., level effect of introduction of PCT testing in ED/AMU)
- $edamu_{it}$ — binary covariate denoting if PCT testing was introduced in ED/AMU by week t in NHS Trust i
- β_3 — indicates the slope change (i.e., trend effect) following the intervention (i.e., PCT testing) in ICU
- $(icu{:}week)_{it}$ — interaction term between time and the intervention in ICU for week t in NHS Trust i
- β_4 — indicates the slope change (i.e., trend effect) following the intervention (i.e., PCT testing) in ED/AMU
- $(edamu{:}week)_{it}$ — interaction term between time and the intervention in ED/AMU for week t in NHS Trust i
- β_5 — denotes the effect of % COVID admissions as a proportion of the total admissions in NHS Trust i in week t
- $(covid\%)_{it}$ — % Covid admissions as a proportion of the total admissions in NHS Trust i in week t
- u_i — denotes an NHS Trust random effect
- ε_{it} — error term

Table S3: Effect sizes estimated by the controlled interrupted time series model of total antibiotic DDDs normalised by admissions (English data). The introduction of NICE rapid guidance NG173 in ISO week 19 (which recommended against use of PCT to guide antibiotic prescribing) is included as a covariate. Both fixed-effect and an interaction term in the model at ISO week 19 are included. Trend and level changes refer to deviations from the overall trend as modelled by the nonlinear smooth term of the generalised additive mixed model.

	Estimate	95% CI	P-value
Level change after PCT introduction in ICU	0.38	(-0.20; 0.97)	0.20
Level change after PCT introduction in ED/AMU	-1.09	(-1.81; -0.38)	0.003
Trend change after PCT introduction in ICU	-0.02	(-0.05; 0.01)	0.21
Trend change after PCT introduction in ED/AMU	0.05	(-0.02; 0.08)	0.003
Level change NICE guidance	14.55	(-21.75; 50.86)	0.43
Trend change NICE guidance	-0.91	(-2.86; 1.03)	0.36
% COVID-positive admissions per total admissions	0.31	(0.28; 0.34)	<0.001

CI – confidence interval; PCT – procalcitonin; ICU – Intensive Care Unit; ED/AMU – Emergency Department/Acute Medical Unit.

Model equation for the model with NICE guidance as a covariate:

$$(DDDs/admissions)_{it} = \beta_0 + f(week)_t + \beta_1 icu_{it} + \beta_2 edamu_{it} + \beta_3 (icu{:}week)_{it} + \beta_4 (edamu{:}week)_{it} + \beta_5 (covid\%)_{it} + \beta_6 nice_t + \beta_7 (nice{:}week)_t + u_i + \varepsilon_{it}, \quad \varepsilon \sim N(0, \sigma^2),$$

where:

- $(DDDs/admissions)_{it}$ — denotes total DDDs, normalised by admissions for an NHS Trust i during week t
- β_0 — denotes the global intercept, representing the baseline level
- $f(week)_t$ — denotes the nonlinear effect of time (cubic spline)
- β_1 — denotes the effect of PCT testing in ICU on total DDDs, normalised by admissions (i.e., level effect of introduction of PCT testing in ICU)
- icu_{it} — binary covariate denoting if PCT testing was introduced in ICU by week t in NHS Trust i
- β_2 — denotes the effect of PCT testing in ED/AMU on total DDDs, normalised by admissions (i.e., level effect of introduction of PCT testing in ED/AMU)
- $edamu_{it}$ — binary covariate denoting if PCT testing was introduced in ED/AMU by week t in NHS Trust i
- β_3 — indicates the slope change (i.e., trend effect) following the intervention (i.e., PCT testing) in ICU
- $(icu{:}week)_{it}$ — interaction term between time and the intervention in ICU for week t in NHS Trust i
- β_4 — indicates the slope change (i.e., trend effect) following the intervention (i.e., PCT testing) in ED/AMU
- $(edamu{:}week)_{it}$ — interaction term between time and the intervention in ED/AMU for week t in NHS Trust i
- β_5 — denotes the effect of % COVID admissions as a proportion of the total admissions in NHS Trust i in week t
- $(covid\%)_{it}$ — % Covid admissions as a proportion of the total admissions in NHS Trust i in week t

- β_6 — denotes the effect of NICE rapid guidance NG173 (i.e., level effect of introduction of the guidance in ISO week 19)
- $nice_t$ — binary covariate denoting if NICE rapid guidance NG173 was in effect in week t
- β_7 — indicates the slope change (i.e., trend effect) following the introduction of NICE rapid guidance NG173
- $(nice{:}week)_t$ — interaction term between time and NICE rapid guidance NG173 for week t
- u_i — denotes an NHS Trust random effect
- ε_{it} — error term

Table S4: Effect sizes estimated by the controlled interrupted time series model of total antibiotic DDDs normalised by admissions with additional step change effects at 4 and 8 weeks (English data). Trend and level changes refer to deviations from the overall trend as modelled by the nonlinear smooth term of the generalised additive mixed model.

	Estimate	95% CI	P-value
Level change after PCT introduction in ICU	0.17	(-0.18; 0.52)	0.34
Level change after PCT introduction in ED/AMU	-0.27	(-0.64; 0.09)	0.14
Level change 4 weeks after PCT introduction in ICU	-0.31	(-0.71; 0.09)	0.13
Level change 4 weeks after PCT introduction in ED/AMU	0.15	(-0.27; 0.57)	0.49
Level change 8 weeks after PCT introduction in ICU	0.06	(-0.36; 0.47)	0.79
Level change 8 weeks after PCT introduction in ED/AMU	0.20	(-0.24; 0.63)	0.37
% COVID-positive admissions per total admissions	0.32	(0.29; 0.34)	<0.001

CI – confidence interval; PCT – procalcitonin; ICU – Intensive Care Unit; ED/AMU – Emergency Department/Acute Medical Unit.

Model equation for the model with step effects at weeks 4 and 8:

$$(DDDs/admissions)_{it} = \beta_0 + f(week)_t + \beta_1 icu_{it} + \beta_2 edamu_{it} + \beta_3 (covid\%)_{it} + \beta_4 icu4w_{it} + \beta_5 icu8w_{it} + \beta_6 edamu4w_{it} + \beta_7 edamu8w_{it} + u_i + \varepsilon_{it}, \quad \varepsilon \sim N(0, \sigma^2),$$

where:

- $(DDDs/admissions)_{it}$ — denotes total DDDs, normalised by admissions for an NHS Trust i during week t
- β_0 — denotes the global intercept, representing the baseline level
- $f(week)_t$ — denotes the nonlinear effect of time (cubic spline)
- β_1 — denotes the effect of PCT testing in ICU on total DDDs, normalised by admissions (i.e., level effect of introduction of PCT testing in ICU)
- icu_{it} — binary covariate denoting if PCT testing was introduced in ICU by week t in NHS Trust i
- β_2 — denotes the effect of PCT testing in ED/AMU on total DDDs, normalised by admissions (i.e., level effect of introduction of PCT testing in ED/AMU)
- $edamu_{it}$ — binary covariate denoting if PCT testing was introduced in ED/AMU by week t in NHS Trust i
- β_3 — denotes the effect of % COVID admissions as a proportion of the total admissions in NHS Trust i in week t
- $\beta_4, \beta_5, \beta_6, \beta_7$ — denotes the delayed effect in ICU and ED/AMU 4 weeks or 8 weeks after the introduction of PCT testing
- $icu4w_{it}, icu8w_{it}, edamu4w_{it}, edamu4w_{it}$ — binary covariate denoting 4 weeks or 8 weeks after the PCT testing was introduced in ICU or ED/AMU by week t in NHS Trust i
- $(covid\%)_{it}$ — % Covid admissions as a proportion of the total admissions in NHS Trust i in week t
- u_i — denotes an NHS Trust random effect
- ε_{it} — error term

Table S5: Effect sizes estimated by the controlled interrupted time series model of total antibiotic DDDs normalised by admissions with Trust size as an additional covariate (English data). The reference category is "Trust type: acute – large". Trend and level changes refer to deviations from the overall trend as modelled by the nonlinear smooth term of the generalised additive mixed model.

	Estimate	95% CI	P-value
Level change after PCT introduction in ICU	0.37	(-0.22; 0.98)	0.22
Level change after PCT introduction in ED/AMU	-1.07	(-1.79; -0.35)	0.004
Trend change after PCT introduction in ICU	-0.02	(-0.05; 0.01)	0.21
Trend change after PCT introduction in ED/AMU	0.05	(0.02; 0.08)	0.004
% COVID-positive admissions per total admissions	0.31	(0.29; 0.34)	<0.001
Trust type: acute – medium	0.27	(-0.78; 1.33)	0.61
Trust type: acute – multiservice	1.03	(-1.22; 3.28)	0.37
Trust type: acute – small	0.04	(-1.00; 3.28)	0.93
Trust type: acute – teaching	-0.47	(-1.47; 0.53)	0.36

CI – confidence interval; PCT – procalcitonin; ICU – Intensive Care Unit; ED/AMU – Emergency Department/Acute Medical Unit.

Model equation for the model with NHS Trust size based on ERIC data from NHS Digital:

$(DDDs/admissions)_{it} = \beta_0 + f(week)_t + \beta_1 icu_{it} + \beta_2 edamu_{it} + \beta_3 (icu{:}week)_{it} + \beta_4 (edamu{:}week)_{it} + \beta_5 (covid\%)_{it} + \beta_6 eric_i + u_i + \varepsilon_{it}, \quad \varepsilon \sim N(0, \sigma^2)$,

where:

- $(DDDs/admissions)_{it}$ — denotes total DDDs, normalised by admissions for an NHS Trust i during week t
- β_0 — denotes the global intercept, representing the baseline level
- $f(week)_t$ — denotes the nonlinear effect of time (cubic spline)
- β_1 — denotes the effect of PCT testing in ICU on total DDDs, normalised by admissions (i.e., level effect of introduction of PCT testing in ICU)
- icu_{it} — binary covariate denoting if PCT testing was introduced in ICU by week t in NHS Trust i
- β_2 — denotes the effect of PCT testing in ED/AMU on total DDDs, normalised by admissions (i.e., level effect of introduction of PCT testing in ED/AMU)
- $edamu_{it}$ — binary covariate denoting if PCT testing was introduced in ED/AMU by week t in NHS Trust i
- β_3 — indicates the slope change (i.e., trend effect) following the intervention (i.e., PCT testing) in ICU
- $(icu{:}week)_{it}$ — interaction term between time and the intervention in ICU for week t in NHS Trust i
- β_4 — indicates the slope change (i.e., trend effect) following the intervention (i.e., PCT testing) in ED/AMU
- $(edamu{:}week)_{it}$ — interaction term between time and the intervention in ED/AMU for week t in NHS Trust i
- β_5 — denotes the effect of % COVID admissions as a proportion of the total admissions in NHS Trust i in week t
- $(covid\%)_{it}$ — % Covid admissions as a proportion of the total admissions in NHS Trust i in week t
- β_6 — denotes the effect of NHS Trust size (based on ERIC categories)
- $eric_i$ — denotes the Trust size (based on ERIC categories) for NHS Trust i
- u_i — denotes an NHS Trust random effect
- ε_{it} — error term

Table S6: Effect sizes estimated by the controlled interrupted time series model of DDDs normalised by admissions (English data), log-transformed. Trend and level changes refer to deviations from the overall trend as modelled by the nonlinear smooth term of the generalised additive mixed model.

	Estimate	95% CI	P-value
Level change after PCT introduction in ICU	0.06	(-0.02; 0.13)	0.16
Level change after PCT introduction in ED/AMU	-0.15	(-0.24; -0.05)	0.002
Trend change after PCT introduction in ICU	-0.004	(-0.01; 0.00)	0.13
Trend change after PCT introduction in ED/AMU	0.01	(0.00; 0.01)	0.004
% COVID-positive admissions per total admissions	0.02	(0.02; 0.02)	<0.001

CI – confidence interval; PCT – procalcitonin; ICU – Intensive Care Unit; ED/AMU – Emergency Department/Acute Medical Unit.

Model equation for the model with a log-transformed dependent variable (DDDs normalised by admissions):

$$log(DDDs/admissions)_{it} = \beta_0 + f(week)_t + \beta_1 icu_{it} + \beta_2 edamu_{it} + \beta_3 (icu{:}week)_{it} + \beta_4 (edamu{:}week)_{it} + \beta_5 (covid\%)_{it} + u_{it} + \varepsilon_{it}, \quad \varepsilon \sim N(0, \sigma^2),$$

where:

- $log(DDDs/admissions)_{it}$ — denotes total DDDs, normalised by admissions for an NHS Trust i during week t, log-transformed
- β_0 — denotes the global intercept, representing the baseline level
- $f(week)_t$ — denotes the nonlinear effect of time (cubic spline)
- β_1 — denotes the effect of PCT testing in ICU on total DDDs, normalised by admissions (i.e., level effect of introduction of PCT testing in ICU)
- icu_{it} — binary covariate denoting if PCT testing was introduced in ICU by week t in NHS Trust i
- β_2 — denotes the effect of PCT testing in ED/AMU on total DDDs, normalised by admissions (i.e., level effect of introduction of PCT testing in ED/AMU)
- $edamu_{it}$ — binary covariate denoting if PCT testing was introduced in ED/AMU by week t in NHS Trust i
- β_3 — indicates the slope change (i.e., trend effect) following the intervention (i.e., PCT testing) in ICU
- $(icu{:}week)_{it}$ + — interaction term between time and the intervention in ICU for week t in NHS Trust i
- β_4 — indicates the slope change (i.e., trend effect) following the intervention (i.e., PCT testing) in ED/AMU
- $(edamu{:}week)_{it}$ + — interaction term between time and the intervention in ED/AMU for week t in NHS Trust i
- β_5 — denotes the effect of % COVID admissions as a proportion of the total admissions in NHS Trust i in week t
- $(covid\%)_{it}$ — % Covid admissions as a proportion of the total admissions in NHS Trust i in week t
- u_i — denotes an NHS Trust random effect
- ε_{it} — error term

Table S7: Effect sizes estimated by the controlled interrupted time series model of DDDs normalised by admissions (English data). Autoregression moving average ARMA(2,1) is included in the model. Trend and level changes refer to deviations from the overall trend as modelled by the nonlinear smooth term of the generalised additive mixed model.

	Estimate	95% CI	P-value
Level change after PCT introduction in ICU	0.35	(-0.32; 1.02)	0.31
Level change after PCT introduction in ED/AMU	-1.14	(-1.95; -0.33)	0.01
Trend change after PCT introduction in ICU	-0.02	(-0.06; 0.02)	0.26
Trend change after PCT introduction in ED/AMU	0.05	(0.01; 0.09)	0.01
% COVID-positive admissions per total admissions	0.31	(0.28; 0.34)	<0.001

CI – confidence interval; PCT – procalcitonin; ICU – Intensive Care Unit; ED/AMU – Emergency Department/Acute Medical Unit.

Model equation with included autoregressive moving average: The model is the same as the main model with included correlation structure for the error term (ARMA(2,1)).

Table S8: Effect sizes estimated by the controlled interrupted time series model of total antibiotic DDDs normalised by occupied overnight bed days (English data). Trend and level changes refer to deviations from the overall trend as modelled by the nonlinear smooth term of the generalised additive mixed model.

	Estimate	95% CI	P-value
Level change after PCT introduction in ICU	0.04	(-0.15; 0.23)	0.681
Level change after PCT introduction in ED/AMU	-0.14	(-0.37; 0.09)	0.234
Trend change after PCT introduction in ICU	-0.0004	(-0.01; 0.01)	0.946
Trend change after PCT introduction in ED/AMU	0.005	(-0.01; 0.02)	0.414
% COVID-positive admissions per total admissions	0.02	(0.02; 0.03)	<0.001

CI – confidence interval; PCT – procalcitonin; ICU – Intensive Care Unit; ED/AMU – Emergency Department/Acute Medical Unit.

Model equation for the model with dependent variable: DDDs normalised by occupied overnight bed days:

$$(DDDs/beddays)_{it} = \beta_0 + f(week)_t + \beta_1 icu_{it} + \beta_2 edamu_{it} + \beta_3 (icu{:}week)_{it} + \beta_4 (edamu{:}week)_{it} + \beta_5 (covid\%)_{it} + u_i + \varepsilon_{it}, \quad \varepsilon \sim N(0, \sigma^2) ,$$

where:

- $(DDDs/beddays)_{it}$ — denotes total DDDs, normalised by bed days for an NHS Trust i during week t
- β_0 — denotes the global intercept, representing the baseline level
- $f(week)_t$ — denotes the nonlinear effect of time (cubic spline)
- β_1 — denotes the effect of PCT testing in ICU on total DDDs, normalised by admissions (i.e., level effect of introduction of PCT testing in ICU)
- icu_{it} — binary covariate denoting if PCT testing was introduced in ICU by week t in NHS Trust i
- β_2 — denotes the effect of PCT testing in ED/AMU on total DDDs, normalised by admissions (i.e., level effect of introduction of PCT testing in ED/AMU)
- $edamu_{it}$ — binary covariate denoting if PCT testing was introduced in ED/AMU by week t in NHS Trust i
- β_3 — indicates the slope change (i.e., trend effect) following the intervention (i.e., PCT testing) in ICU
- $(icu{:}week)_{it}$ — interaction term between time and the intervention in ICU for week t in NHS Trust i
- β_4 — indicates the slope change (i.e., trend effect) following the intervention (i.e., PCT testing) in ED/AMU
- $(edamu{:}week)_{it}$ — interaction term between time and the intervention in ED/AMU for week t in NHS Trust i
- β_5 — denotes the effect of % COVID admissions as a proportion of the total admissions in NHS Trust i in week t
- $(covid\%)_{it}$ — % Covid admissions as a proportion of the total admissions in NHS Trust i in week t
- u_i — denotes an NHS Trust random effect
- ε_{it} — error term

Table S9: Effect sizes estimated by the controlled interrupted time series model of CAP DDDs normalised by admissions (English data). Trend and level changes refer to deviations from the overall trend as modelled by the nonlinear smooth term of the generalised additive mixed model.

	Estimate	95% CI	P-value
Level change after PCT introduction in ICU	0.17	(-0.23; 0.56)	0.42
Level change after PCT introduction in ED/AMU	-0.67	(-1.16; -0.19)	0.01
Trend change after PCT introduction in ICU	-0.01	(-0.03; 0.01)	0.34
Trend change after PCT introduction in ED/AMU	0.03	(0.01; 0.05)	0.01
% COVID-positive admissions per total admissions	0.25	(0.24; 0.27)	<0.001

CI – confidence interval; PCT – procalcitonin; ICU – Intensive Care Unit; ED/AMU – Emergency Department/Acute Medical Unit.

Model equation for the model with dependent variable: CAP DDDs normalised by admissions:

$$(CAP\ DDDs/admissions)_{it} = \beta_0 + f(week)_t + \beta_1 icu_{it} + \beta_2 edamu_{it} + \beta_3 (icu{:}week)_{it} + \beta_4 (edamu{:}week)_{it} + \beta_5 (covid\%)_{it} + u_i + \varepsilon_{it}, \quad \varepsilon \sim N(0, \sigma^2)\ ,$$

where:

- $(CAP\ DDDs/admissions)_{it}$ — denotes CAP DDDs, normalised by admissions for an NHS Trust i during week t
- β_0 — denotes the global intercept, representing the baseline level
- $f(week)_t$ — denotes the nonlinear effect of time (cubic spline)
- β_1 — denotes the effect of PCT testing in ICU on total DDDs, normalised by admissions (i.e., level effect of introduction of PCT testing in ICU)
- icu_{it} — binary covariate denoting if PCT testing was introduced in ICU by week t in NHS Trust i
- β_2 — denotes the effect of PCT testing in ED/AMU on total DDDs, normalised by admissions (i.e., level effect of introduction of PCT testing in ED/AMU)
- $edamu_{it}$ — binary covariate denoting if PCT testing was introduced in ED/AMU by week t in NHS Trust i
- β_3 — indicates the slope change (i.e., trend effect) following the intervention (i.e., PCT testing) in ICU
- $(icu{:}week)_{it}$ + — interaction term between time and the intervention in ICU for week t in NHS Trust i
- β_4 — indicates the slope change (i.e., trend effect) following the intervention (i.e., PCT testing) in ED/AMU
- $(edamu{:}week)_{it}$ + — interaction term between time and the intervention in ED/AMU for week t in NHS Trust i
- β_5 — denotes the effect of % COVID admissions as a proportion of the total admissions in NHS Trust i in week t
- $(covid\%)_{it}$ — % Covid admissions as a proportion of the total admissions in NHS Trust i in week t
- u_i — denotes an NHS Trust random effect
- ε_{it} — error term

Table S10: Effect sizes estimated by the controlled interrupted time series model of CAP DDDs normalised by occupied overnight bed days (English data). Trend and level changes refer to deviations from the overall trend as modelled by the nonlinear smooth term of the generalised additive mixed model.

	Estimate	95% CI	P-value
Level change after PCT introduction in ICU	0.01	(-0.11; 0.13)	0.87
Level change after PCT introduction in ED/AMU	-0.09	(-0.25; 0.06)	0.22
Trend change after PCT introduction in ICU	-0.0003	(-0.01; 0.01)	0.93
Trend change after PCT introduction in ED/AMU	0.003	(-0.004; 0.01)	0.46
% COVID-positive admissions per total admissions	0.03	(0.03; 0.04)	<0.001

CI – confidence interval; PCT – procalcitonin; ICU – Intensive Care Unit; ED/AMU – Emergency Department/Acute Medical Unit.

Model equation for the model with dependent variable: CAP DDDs normalised by occupied overnight bed days:

$$(CAP\ DDDs/beddays)_{it} = \beta_0 + f(week)_t + \beta_1 icu_{it} + \beta_2 edamu_{it} + \beta_3 (icu{:}week)_{it} + \beta_4 (edamu{:}week)_{it} + \beta_5 (covid\%)_{it} + u_i + \varepsilon_{it},\ \ \varepsilon \sim N(0, \sigma^2)\ ,$$

where:

- $(CAP\ DDDs/beddays)_{it}$ — denotes CAP DDDs, normalised by occupied overnight bed days for an NHS Trust i during week t
- β_0 — denotes the global intercept, representing the baseline level
- $f(week)_t$ — denotes the nonlinear effect of time (cubic spline)
- β_1 — denotes the effect of PCT testing in ICU on total DDDs, normalised by admissions (i.e., level effect of introduction of PCT testing in ICU)
- icu_{it} — binary covariate denoting if PCT testing was introduced in ICU by week t in NHS Trust i
- β_2 — denotes the effect of PCT testing in ED/AMU on total DDDs, normalised by admissions (i.e., level effect of introduction of PCT testing in ED/AMU)
- $edamu_{it}$ — binary covariate denoting if PCT testing was introduced in ED/AMU by week t in NHS Trust i
- β_3 — indicates the slope change (i.e., trend effect) following the intervention (i.e. PCT testing) in ICU
- $(icu{:}week)_{it}$ — interaction term between time and the intervention in ICU for week t in NHS Trust i
- β_4 — indicates the slope change (i.e., trend effect) following the intervention (i.e. PCT testing) in ED/AMU
- $(edamu{:}week)_{it}$ — interaction term between time and the intervention in ED/AMU for week t in NHS Trust i
- β_5 — denotes the effect of % COVID admissions as a proportion of the total admissions in NHS Trust i in week t
- $(covid\%)_{it}$ — % Covid admissions as a proportion of the total admissions in NHS Trust i in week t
- u_i — denotes an NHS Trust random effect

- ε_{it} — error term

Supplementary figures

Figure S1: Violin plots for the overall antibiotic use (DDDs) and DDDs normalised by admission for the studied NHS Trusts (English data)
(a) Overall antibiotic use (DDDs) per week by PCT user status (b) Overall DDDs normalised by admissions per week per NHS Trust by PCT user status

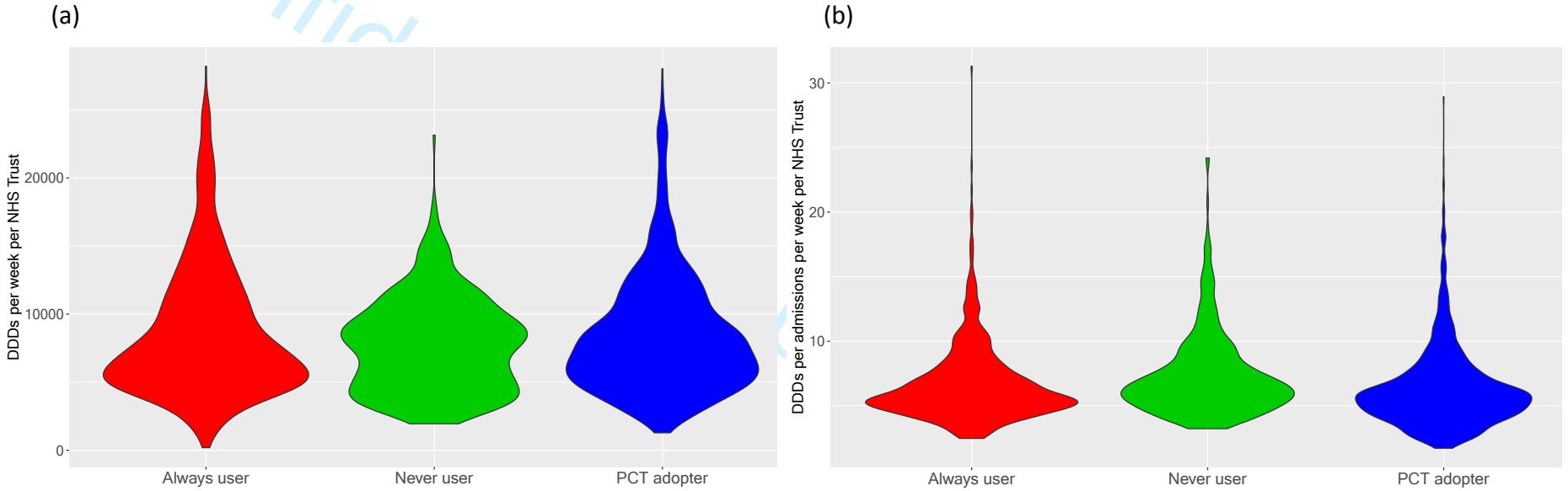


Figure S2: Mean of the main variables during the first wave of the COVID-19 pandemic for the studied NHS Trusts (English data)
(a) DDDs per week per NHS Trust (b) Number of admissions per week per NHS Trust (c) Number of occupied overnight bed days per week per NHS Trust (d) Number of COVID-19 admissions per week per NHS Trust

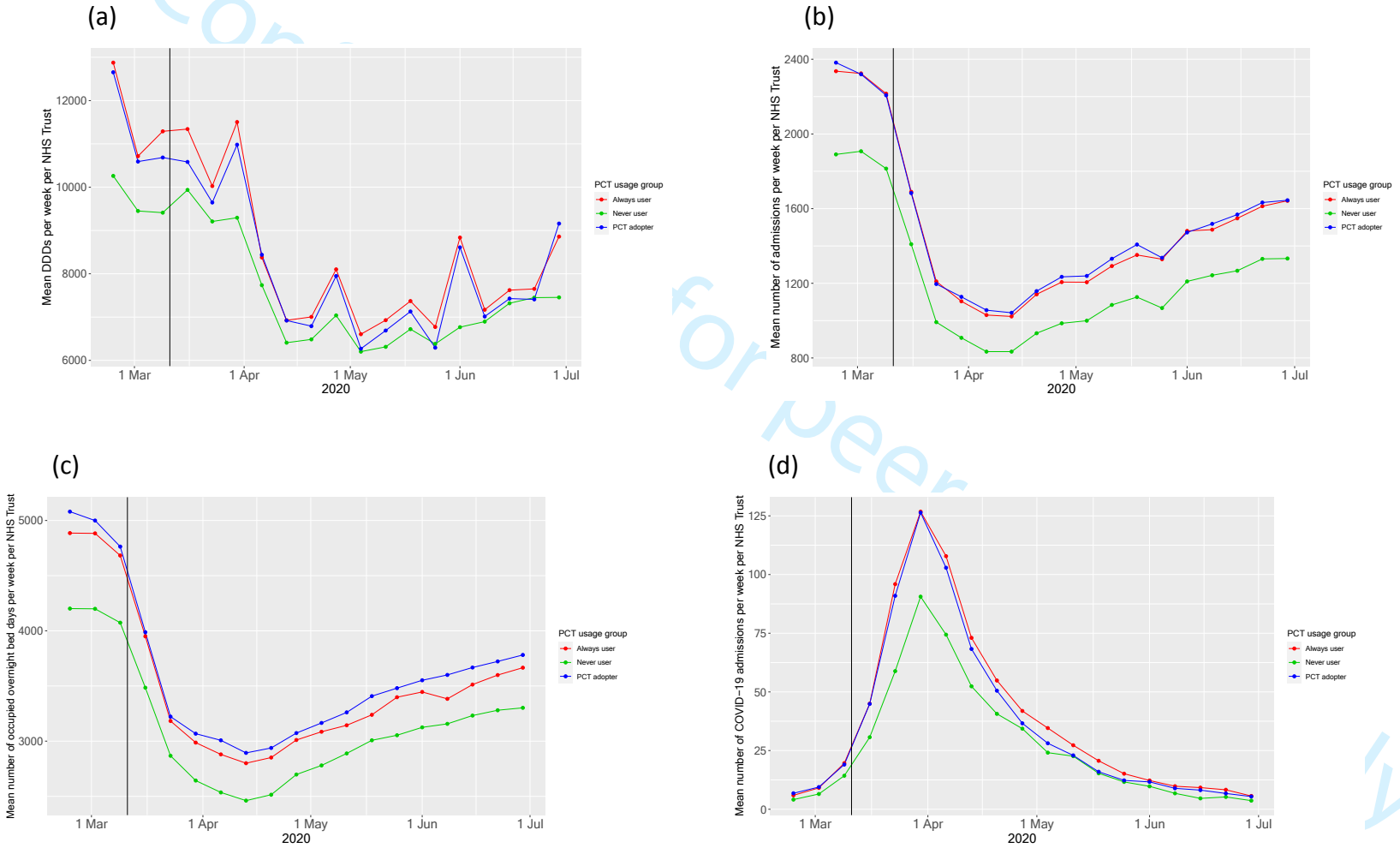


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Figure S3: Main variables during the first wave of the COVID-19 pandemic for the studied NHS Trusts (English data) presented as one line per NHS Trust
(a) DDDs per week per NHS Trust (b) Number of admissions per week per NHS Trust (c) Number of occupied overnight bed days per week per NHS Trust (d) Number of COVID-19 admissions per week per NHS Trust

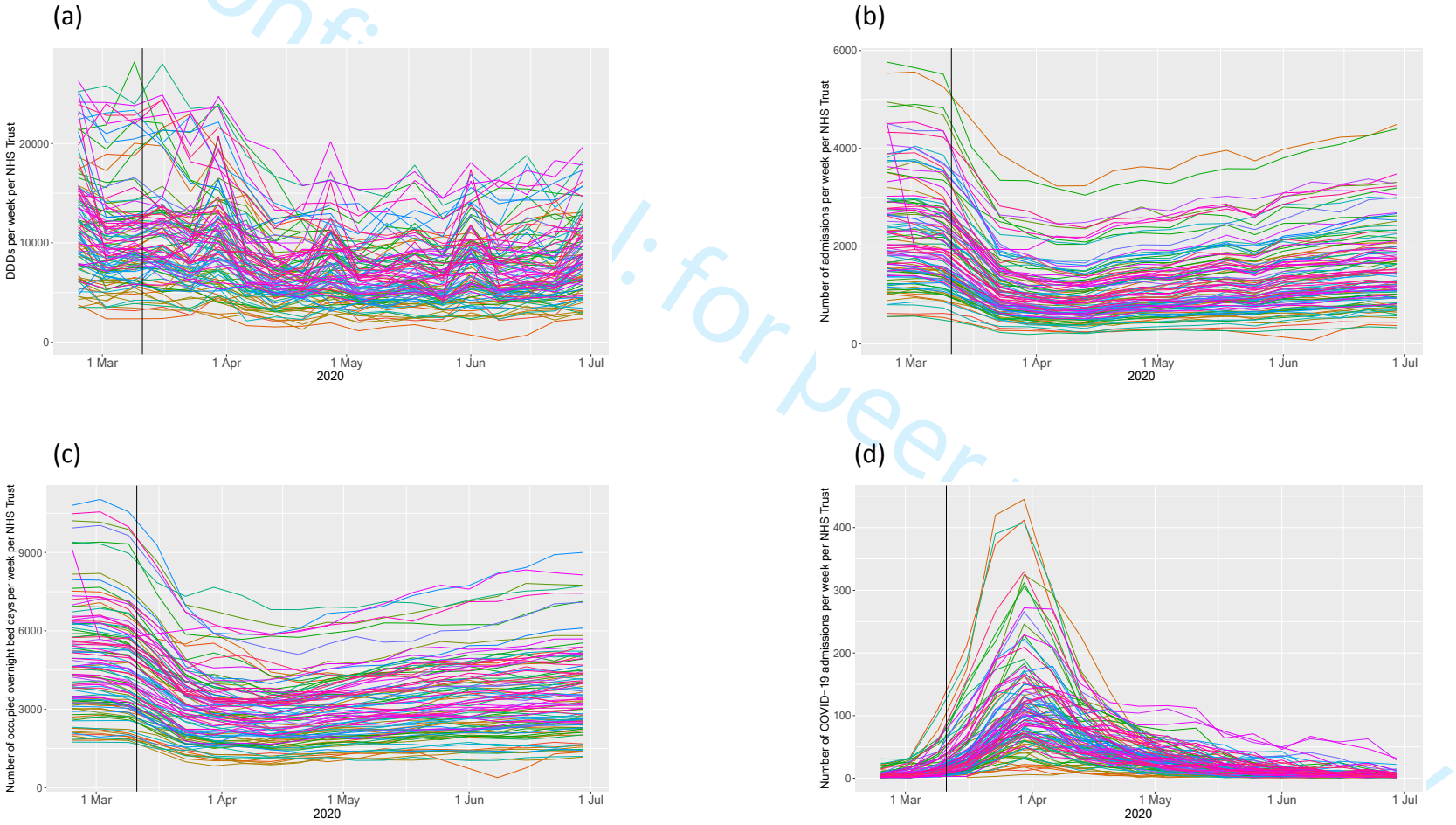

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Figure S4: Main variables during the first wave of the COVID-19 pandemic for the studied NHS Trusts (English data) and the Welsh hospitals (a) Mean DDDs normalised by admissions per week per NHS Trust/hospital (b) Mean DDDs normalised by occupied overnight bed days per week per NHS Trust/hospital (c) Mean DDDs normalised by COVID-19 admissions per week per NHS Trust/hospital (d) Mean DDDs normalised by occupied overnight COVID-19 bed days per week per NHS Trust/hospital

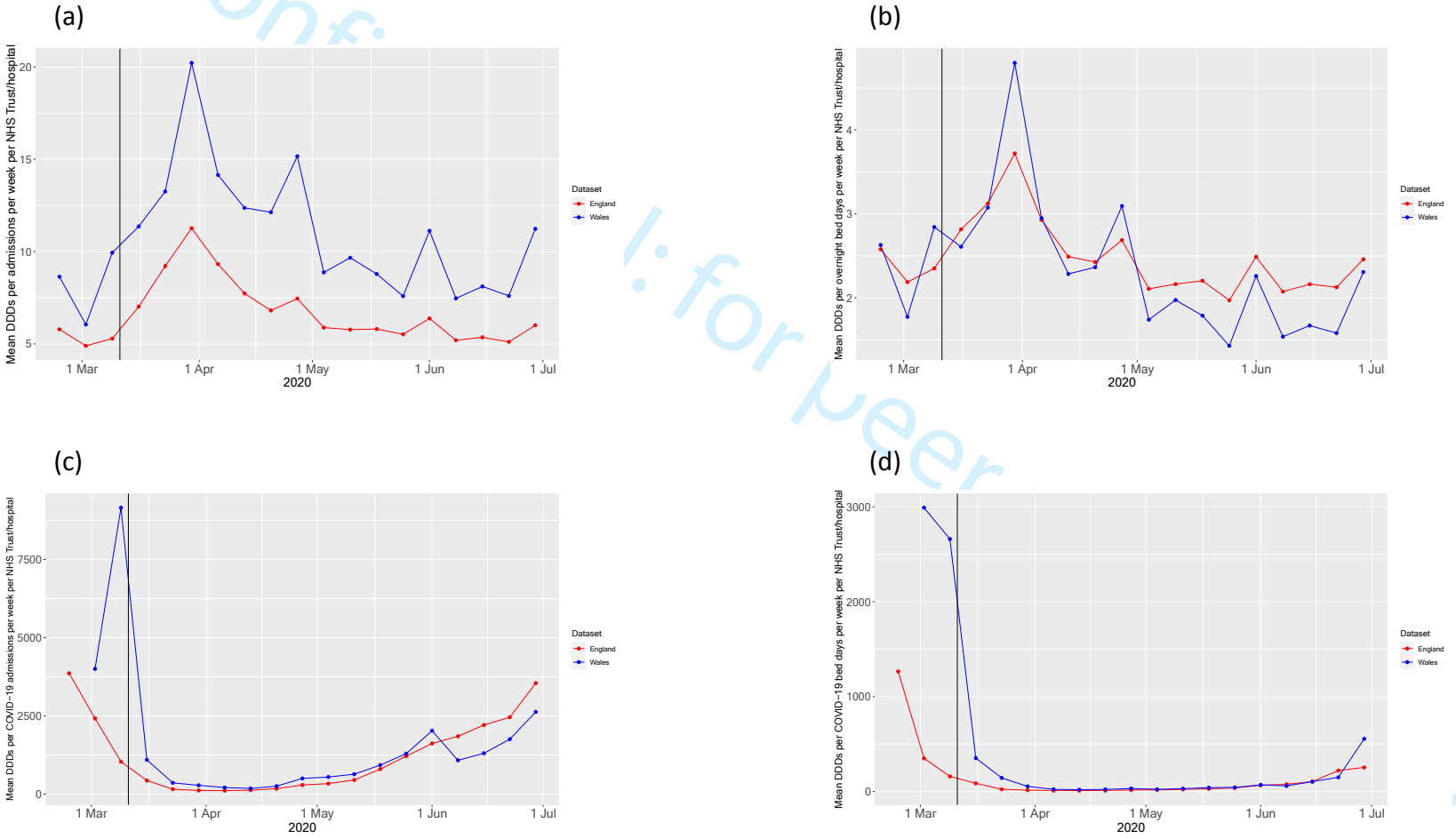

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Figure S5: DDDs per admissions per week per NHS Trust for all NHS Trusts separately. The introduction of PCT testing in the relevant NHS Trusts, which started to use the test during the 1st COVID-19 wave is depicted with change of colour