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Synopsis

Procalcitonin evaluation of antibiotic use in COVID-19 hospitalised patients: The PEACH mixed methods study

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Abstract

Background: Early in the COVID-19 pandemic, there was concern about potentially unnecessary antibiotic prescribing in the National Health Service. Procalcitonin testing was being used in some hospitals to guide antibiotic use. This study aimed to investigate the impact of procalcitonin testing on United Kingdom's antibiotic prescribing and health outcomes.

Methods: Mixed-methods study comprising quantitative, qualitative and health economic work packages, including a:

1. survey of National Health Service hospitals to understand procalcitonin use
2. retrospective, controlled, interrupted time series analysis of aggregated, organisation-level data, including antibiotic dispensing, hospital activity and procalcitonin testing from acute hospital trusts/hospitals in England/Wales. Primary outcome: change in level and/or trend of antibiotic prescribing rates following introduction of procalcitonin
3. multicentre, retrospective, cohort study of 5960 patients using patient-level clinical data from 11 trusts/health boards to determine the difference in early antibiotic prescribing between COVID-19 patients who did/did not have baseline procalcitonin testing by using propensity score matching. Primary outcome: days of early antibiotic therapy
4. qualitative study exploring the decision-making process around antibiotic use for inpatients with COVID-19 pneumonia to identify the contextual factors, feasibility and acceptability of procalcitonin testing algorithms
5. health economic analysis evaluating the cost-effectiveness of baseline procalcitonin testing using the matched data within a decision-analytic model.

Setting: Acute hospital trusts/health boards in England/Wales.

Participants: Inpatients ≥ 16 years, admitted to participating trusts/health boards and with a confirmed positive COVID-19 test between 1 February 2020 and 30 June 2020, National Health Service healthcare workers.

Results: Early in the COVID-19 pandemic, procalcitonin use was expanded/introduced in many National Health Service hospitals, with variation in guidance and interpretation of results. The number of hospitals using procalcitonin in emergency/acute admissions rose from 17 (11%) to 74/146 (50.7%), and its use in intensive care unit increased from 70 (47.6%) to 124/147 (84.4%). Introduction of procalcitonin testing in emergency departments/acute medical admission units was associated with a statistically significant decrease in antibiotic use, which was not sustained. Patient-level data showed that baseline procalcitonin testing was associated with an average reduction in early antibiotic prescribing of 0.43 days (95% confidence interval: 0.22 to 0.64 days, $p < 0.001$) and a reduction of 0.72 days (95% confidence interval: 0.06 to 1.38 days, $p = 0.03$) in total antibiotic prescribing, with no increased mortality/hospital length of stay. Interviews revealed concerns about secondary bacterial infections that led to increased antibiotic prescribing in COVID-19 patients. As experience increased, clinician's ability to distinguish between COVID-19 alone and bacterial coinfections increased. Antibiotic prescribing decisions were influenced by factors such as senior support, situational factors and organisational influences. The health economic analysis concluded that baseline procalcitonin testing was more likely to be cost-effective than not, albeit with some uncertainty.

Conclusion: Baseline procalcitonin testing appears to have been an effective antimicrobial stewardship tool during the first wave of the pandemic, reducing antibiotic prescribing without evidence of harm.

Limitations: The retrospective, hospital record-based studies were limited by missing data, incorrectly recorded information and lack of randomisation. Interviews with clinicians were conducted more than a year after the first wave, potentially resulting in recall bias.

Future work: This study highlights the need for adaptive, inclusive, wide-reaching trials of infection diagnostics and implementation research to assess clinical utility before routine introduction into clinical practice.

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A plain language summary of this synopsis is available on the NIHR Journals Library Website https://doi.org/10.3310/GGFF9393.

Synopsis

This report details work undertaken to assess whether the use of procalcitonin (PCT) testing helped to safely reduce antibiotic use among patients who were hospitalised and had coronavirus disease discovered in 2019 during the first wave of the pandemic. It arose from a commissioned call by the National Institute for Health and Care Research (NIHR) COVID Recovery and Learning call to better understand and manage the health and social care consequences of the global COVID-19 pandemic beyond the acute phase. The study results were delayed by unavoidable difficulties in collecting retrospective data from routine hospital records (paper and electronic), and in data cleaning and analysis, which meant that the results were not able to inform subsequent waves of the pandemic but are useful for generalisable learning, including for the management of current COVID-19 and other respiratory infections in adults in the UK.

Background

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the novel virus that caused the recent pandemic of illness called as COVID-19. The pandemic phase is over, but people continue to be admitted to hospital and intensive care units (ICUs) with COVID-19. Although the majority of patients affected by COVID-19 have experienced mild illness, a large number of people have been admitted to hospital.[2] Many patients required oxygen therapy via positive pressure ventilation and some required mechanical ventilation on intensive care.[2] SARS-CoV-2 is a virus, and antibacterial agents (antibiotics) therefore have no direct antimicrobial effect on it. In spite of this, many patients (45–100%) with COVID-19 were prescribed with antibiotics.[3–9] Empirical antibiotic therapy was recommended in the World Health Organization (WHO) guidelines for patients with suspected or confirmed severe COVID-19, COVID-19-related sepsis and community- and hospital-acquired pneumonia.[2] The evidence base to support this practice was limited, and recommendations were based on concerns that patients may experience secondary bacterial infections that may respond to antibiotic therapy.

At a time when accumulating antibiotic resistance was increasingly acknowledged as a global threat to health, the COVID-19 pandemic had the worrying potential to drive unnecessary antibiotic use.[10] Antibiotic prescribing for patients, who do not need them, unnecessarily drives excess mortality, for example through selection for resistant pathogens, *Clostridioides* (*Clostridium*) *difficile* infection and adverse drug reactions. There is an indirect evidence of unnecessary antibiotic prescribing during the COVID-19 pandemic.[11] Published data indicate that rates of secondary bacterial infection were low at 7–15%,[3,7,8,11,12] and many confirmed secondary bacterial infections occurred late in the illness. Crucially, therefore, there was a big difference between the number of patients with second ary bacterial infection and the number receiving antibiotics, particularly early in the course of infection, indicating that more studies are needed to guide appropriate antibiotic use.

Procalcitonin is an inflammatory marker that can be measured in blood samples and is widely recommended to help diagnose bacterial infections and guide antibiotic treatment.[13] However, reviews of evidence to support use of PCT in respiratory infections before the COVID-19 pandemic found conflicting results.[14,15] Early in the pandemic, local guidelines were developed in several NHS hospitals, which advised the use of PCT testing to assist in the decision to start or stop antibiotics in patients with COVID-19, but other NHS hospitals did not adopt this approach. In the absence of high-quality evidence in this clinical context, the use of PCT was pragmatic and its impact requires evaluation. A key question is whether such testing impacted on the antibiotic use, length of stay (LOS), ICU admission, resistant infections and mortality. Several randomised controlled trials (RCTs) (ADAPT-Sepsis, PRONTO and BATCH) have either completed recruitment or are nearing completion to assess the impact of PCT testing on antibiotic use, but these are not specifically focused on COVID-19 patients. The aim of the project was to conduct a rapid assessment of the utility of PCT testing in COVID-19 to inform care during any subsequent waves of infection and to make interim recommendations using the best available evidence.

Protocol

The main aim of the Procalcitonin Evaluation of Antibiotic use in COVID-19 Hospitalised patients (PEACH) study was to assess whether the use of PCT testing to guide antibiotic prescribing safely reduced antibiotic use among patients who were hospitalised and suffered with COVID-19 during the first wave of the pandemic – in order to inform care during any subsequent waves of infection

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and to make interim recommendations using the best available evidence. Only observational (retrospective) and qualitative studies were open to us during the recovery and learning period. A mixed-methods approach was designed to answer the research questions. Because of the limitations of retrospective observational data, two quantitative work packages (WPs) were delivered – one using patient-level data, and the other using aggregated hospital data.

Three different, and complimentary, work streams (WSs) were carried out, containing discrete WPs as follows:

Work stream 1: utilisation of PCT testing to guide antibiotic prescribing during the first wave of COVID-19 pandemic.
Work stream 2: patient-level impact of PCT testing on antibiotic exposure and clinical outcome (main WS).
Work stream 3: health economics analysis of PCT testing to guide antibiotic prescribing in those admitted to hospital and positive for COVID-19.

Full details of the proposed study in WP 2.1 and the analysis plan were published as a protocol,[16] and the interrelationships between the three WSs are summarised in *Figure 1*. The project website, that gives an overall summary of the study, is provided in supplementary information to complement this report. The PEACH study, including all WSs in this report, was prospectively registered with the International Standard Randomised Controlled Trial Number registry as IRCTN66682918. Protocol v1.1 02.03.21 was the original protocol approved by the Research Ethics Committee. The current approved PEACH protocol is v1.2 25.08.22, following a non-substantial protocol amendment to update the list of secondary outcomes.

Work stream 1: utilisation of procalcitonin testing to guide antibiotic prescribing during the first wave of the COVID-19 pandemic

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This WS was divided into two separate WPs (see *Figure 1*).

Work package 1.1: describing how acute National Health Service hospitals used procalcitonin during the first wave of COVID-19

The findings of this WP were published in *Antibiotics*.[1] The aim of the study was to describe the use of PCT in English and Welsh hospitals during the first wave of the COVID-19 pandemic (defined as from 24 February to 5 July 2020). A web-based survey was sent to antimicrobial leads in all NHS Trusts/Health Boards in England and Wales to gather data on PCT use prior to the pandemic and how it was introduced during it. A descriptive report was produced detailing whether PCT was adopted during the pandemic; and, if so, in which areas of the hospital [ICU, emergency department (ED), acute medical unit (AMU)], PCT cut-offs, the testing algorithm, whether PCT was part of a hospital guideline or biochemistry order set, whether participants thought PCT was useful in efforts to control antibiotic overuse and whether participants plan to use PCT as part of their antibiotic stewardship program after the first COVID-19 wave. Results revealed that during the first wave of the COVID-19 pandemic, there was widespread introduction and expansion of PCT use in NHS hospitals. The number of hospitals using PCT in emergency/acute admissions rose from 17 (11%) to 74/146 (50.7%), and its use in the ICU increased from 70 (47.6%) to 124/147 (84.4%). This increase happened predominantly in March and April 2020, preceding National Institute for Health and Care Excellence (NICE) guidance. Approximately, half of hospitals reported using PCT as a single test to guide decisions to discontinue antibiotics, and half reported use of repeated measurements. There was a marked variation in the thresholds used for empiric antibiotic cessation and guidance about the interpretation of values (*Table 1*). PCT testing was widely adopted in the NHS during the COVID-19 pandemic in an unevidenced, heterogeneous way and in conflict with the relevant NICE guidance. Further research is needed urgently that assesses the impact of this change on antibiotic prescribing and patient safety.

Work package 1.2: organisational-level impact of procalcitonin on antibiotic use

The findings of this WP were published in the *Journal of Antimicrobial Chemotherapy*.[17] The aim of the study was to determine whether, at an NHS Trust level, having used or introduced PCT testing during COVID-19 was associated with changes in antibiotic use. We conducted a multicentre, retrospective, controlled interrupted time series analysis of aggregated, organisation-level data from acute hospitals/hospital trusts in England and Wales during the first wave of COVID-19 (*Figure 2*). Three data sets describing antibiotic dispensing, hospital activity and PCT testing

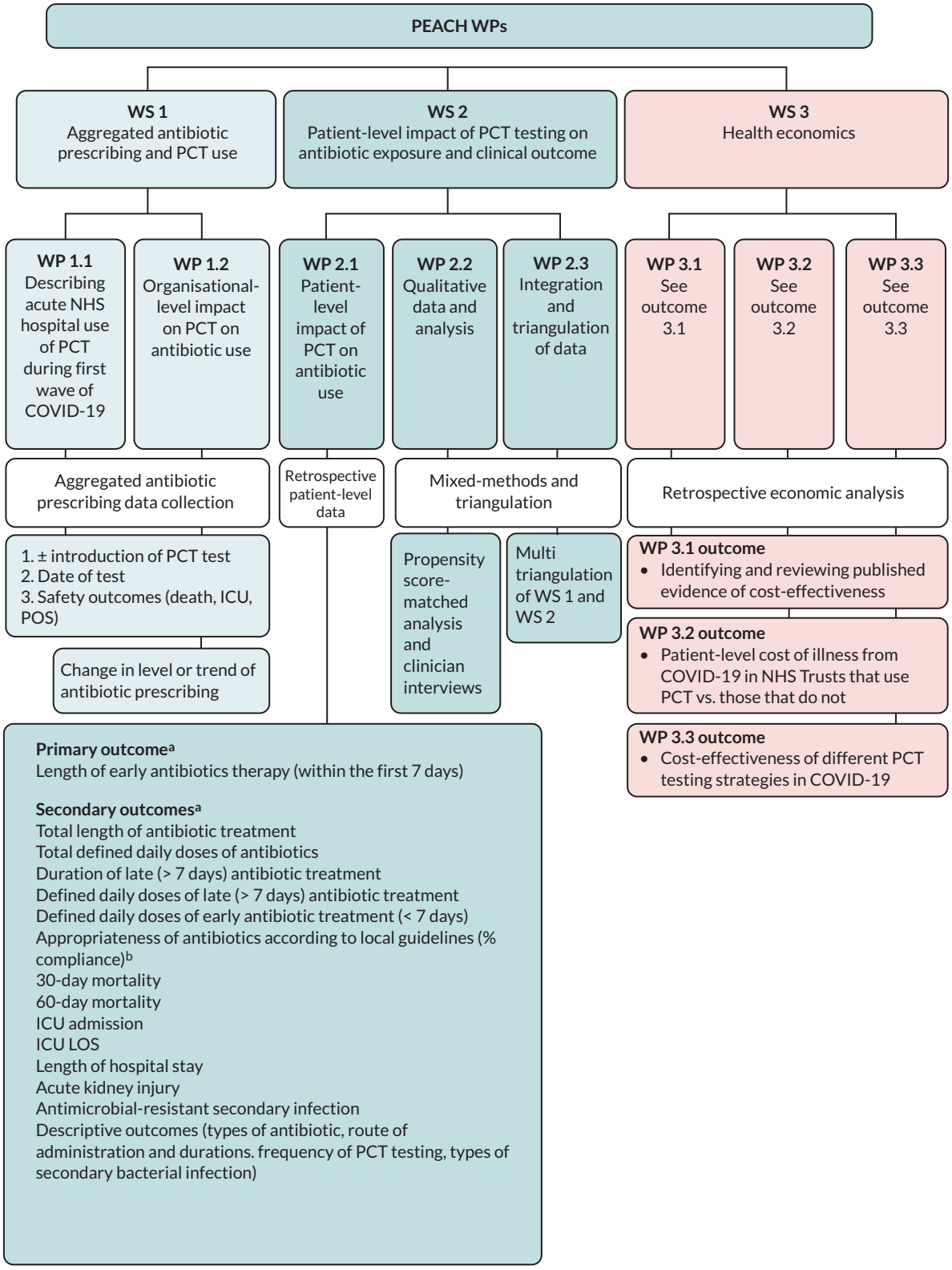

FIGURE 1 Overview of WSs in the PEACH study. a, For centres USING and NOT USING PCT routinely; b, if practicable. POS, Palliative Outcome Score. Reproduced with permission from Euden *et al.*[16] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

TABLE 1 Nature of PCT use to support antibiotic prescribing during first wave of COVID-10 pandemic in England and Wales

	ICU	Non-ICU
Cut-off (ng/ml)	*n* = 116	*n* = 78
0.1	1 (1%)	0
0.2	1 (1%)	0
0.25	51 (44%)	41 (53%)
0.5	54 (47%)	27 (35%)
No cut-off specified, cut-off varied dependent on clinical context	9 (8%)	10 (13%)
Timing	*n* = 114	*n* = 76
Single measurement	14 (12%)	39 (51%)
Two measurements	23 (20%)	21 (28%)
Serial	72 (63%)	9 (12%)
Other	5 (4%)	7 (9%)
Biochemistry order set	*n* = 122	*n* = 107
Yes	50 (41%)	33 (31%)
Hospital guideline	*n* = 114	
PCT part of a hospital guideline for managing COVID-19	55 (48%)	

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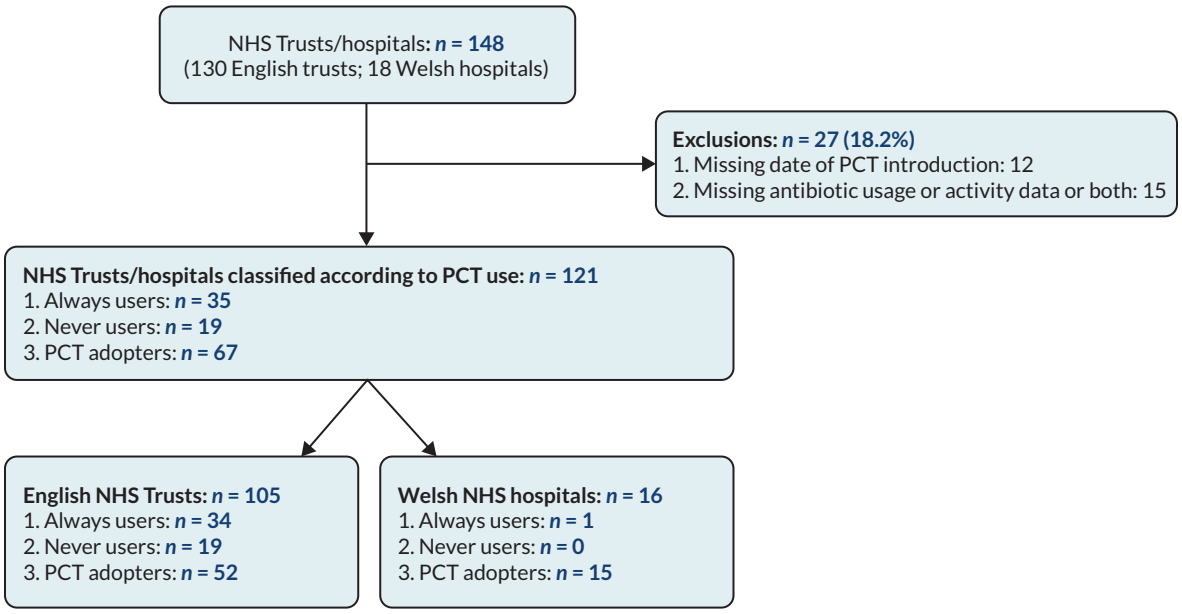

FIGURE 2 Number of NHS trusts/hospitals included in the WP 1.2 analysis classified according to their PCT usage before and during the first wave of the COVID-19 pandemic in the UK. Reproduced with permission from Llewelyn *et al.*[17] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build up on this work, for commercial use, provided the original work is properly cited. See https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original.

data were gathered through our partners Rx-Info Ltd, Public Health England and Public Health Wales and for analysis. To reduce the risk of bias, we attempted to collect data from all acute NHS Trusts/hospitals. If data were excluded from the final analysis, the reason for the exclusion was reported (see *Figure 2*). All data were collected by separate team members, and analysis was performed by team members not involved in data collection. The three data sets were merged to create a single analysis data set by matching the NHS Organisational Data Service Trust/hospital codes in the respective data sets. We anticipated that the analysis could have potentially been confounded by multiple factors, including changes in antibiotic prescribing over time, in addition to changes in number of COVID-19 admissions over time, the introduction of NICE guidance NG173 and the size of NHS Trusts/hospitals. Using the available data sets, only the listed confounding factors could be included either in the primary model or sensitivity analyses; variation, for example, in how individual clinicians or departments used antibiotics could not be accounted for using this approach. Data collection and analysis were pre-specified in our PEACH statistical analysis plan, which can be found in the supplementary data in the published paper.

The primary outcome was a change in the level and/or trend of antibiotic prescribing rates following the introduction of PCT testing [weekly trend of number of defined daily doses (DDDs) of pre-specified antibiotics commonly used for respiratory tract infection or community-acquired pneumonia ('CAP-DDD') per number of COVID-positive admissions]. 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. Trusts/hospitals were categorised as follows: 'always users' – if PCT testing was in use prior to the first wave of COVID-19 and continued to be used 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. Our results showed that, in the main analysis of 105 hospitals in England, introduction of PCT testing in ED/AMUs was associated with a statistically significant decrease in the total antibiotic use of −1.08 [95% confidence interval (CI): −1.81 to −0.36] DDDs of antibiotic per admission per week per trust (*Figure 3*). This effect was then lost at a rate of 0.05 (95% CI 0.02 to 0.08) DDDs per admission per week. Similar results were found specifically for first-line antibiotics for CAP and for COVID-19 admissions rather than all admissions. Introduction of PCT in the ICU setting was not associated with any significant change in antibiotic use. In hospitals where PCT testing was introduced in ED/AMU, this was associated with an initial, but unsustained, reduction in antibiotic use.

Work stream 2: patient-level impact of procalcitonin testing on antibiotic exposure and clinical outcome

This WS focused on patient-level data and was divided into three separate WPs (see *Figure 1*).

Work package 2.1: assessing the patient-level impact of procalcitonin on antibiotic use

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The findings of this WP were published in the *Journal of Antibiotic Chemotherapy*.[18] This was the main WP in the wider PEACH study, and the aim was to investigate the impact of PCT testing on antibiotic prescribing and health outcomes. We conducted a multicentre, retrospective, cohort study using patient-level clinical data from patients at 11 acute hospital trusts/health boards in England and Wales. Patient characteristics can be seen in *Table 2*. Rates of PCT use in COVID-19 patients varied considerably between these sites, as reported in WP 1.1.[1] Potentially eligible patients were identified from institutional databases/medical records by the clinical teams at each participating organisation. The inclusion criteria were patients aged ≥ 16 years, admitted to participating trusts/health boards and with a confirmed positive COVID-19 test between 1 February 2020 and 30 June 2020. Exclusion criteria were second and subsequent admissions after index admission with COVID-19. The primary objective was to measure the difference in early antibiotic prescribing (≤ 7 days after a first positive COVID-19 test) between COVID-19 patients who did/did not have baseline PCT testing (performed on day ±1 of COVID-19 test). Secondary objectives were to measure the differences in LOS, mortality and ICU admission. Consecutive patients fulfilling the eligibility criteria were included in the analysis to reduce the risk of bias. Identification of subjects was carried out without prior knowledge of outcomes or PCT testing status and by separate teams from those performing the

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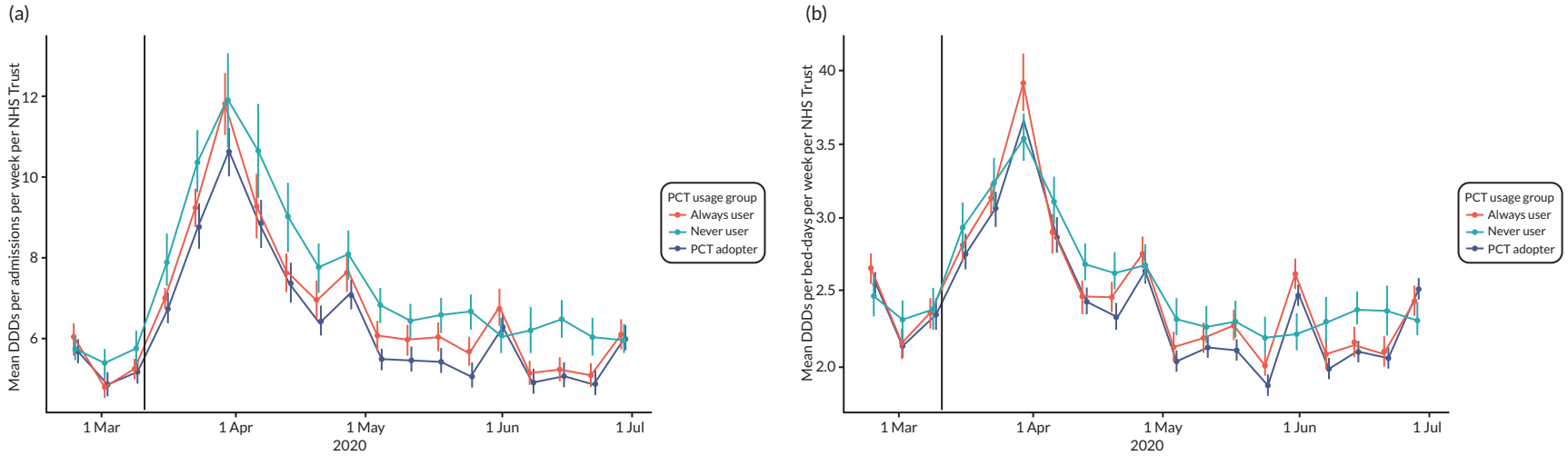

FIGURE 3 Antibiotic use at 105 NHS Trusts in England during the first wave of the COVID-19 pandemic according to PCT use. Figures show mean antibiotic use per week per NHS Trust by PCT usage. (a) Antibiotic DDDs per admission per week. (b) Mean antibiotic DDDs per occupied overnight bed-days per week. The error bars in (a) and (b) show the corresponding 95% CIs. The vertical black lines represent 11 March 2020 when the WHO declared the novel coronavirus outbreak as a global pandemic. Reproduced with permission from Llewelyn *et al.*[17] The figure includes minor additions and formatting changes to the original text.

analysis. Potential confounding factors for inclusion in the propensity score analysis, that is those potentially influencing both the outcomes and the decision to use PCT testing, were agreed in advance of the analysis and were published in our protocol paper.[16] Objective criteria for study variables were agreed in advance. Data from 5960 patients were analysed (*Figure 4*). One thousand five hundred and forty-eight patients (26.0%) had a baseline PCT test and 4412 (74.0%) did not. To assess the effect of PCT testing on antibiotic prescribing and patient outcomes, while ensuring an even distribution of important confounders between groups, propensity score matching was used. Patients who did or did not receive PCT testing at baseline were matched. The matching was used to reduce potential differences between the 'tested' [average effect of testing on the tested (ATT)] (i.e. PCT test at baseline) and 'untested' [average effect of testing on the untested (ATU)] patient (i.e. no PCT test at baseline) populations using characteristics deemed prognostic of clinical endpoints. Using the data generated from the propensity score matching, regression modelling was used to examine whether the baseline PCT testing affected antibiotic prescribing and other outcomes.

The mean number of days of early antibiotics in the matched data was 3.96 (standard deviation 2.53). *Figures 5* and *6* show the spread of the number of days of early antibiotic therapy in the primary (ATT) and secondary (ATU) analyses, broken down by the PCT test status at baseline.

Results showed that baseline PCT testing was associated with an average reduction in early antibiotic prescribing of 0.43 days (95% CI 0.22 to 0.64 days, $p < 0.001$) per patient who had PCT testing at baseline compared to a (hypothetical) scenario in which they did not. A similar significant decrease of 0.30 days (standard error = 0.10, 95% CI 0.11 to 0.49, $p = 0.002$) was estimated in the secondary (ATU) analysis. The estimated average effect of PCT testing at baseline on total antibiotic prescribing was a decrease of 0.72 days (95% CI 0.06 to 1.38 days, $p = 0.03$), indicating that the average effect of testing was to decrease the duration of total antibiotics by 0.72 days per tested patient compared to a (hypothetical) scenario with no testing.

There was no evidence that baseline PCT testing was associated with increased mortality or hospital/ICU LOS

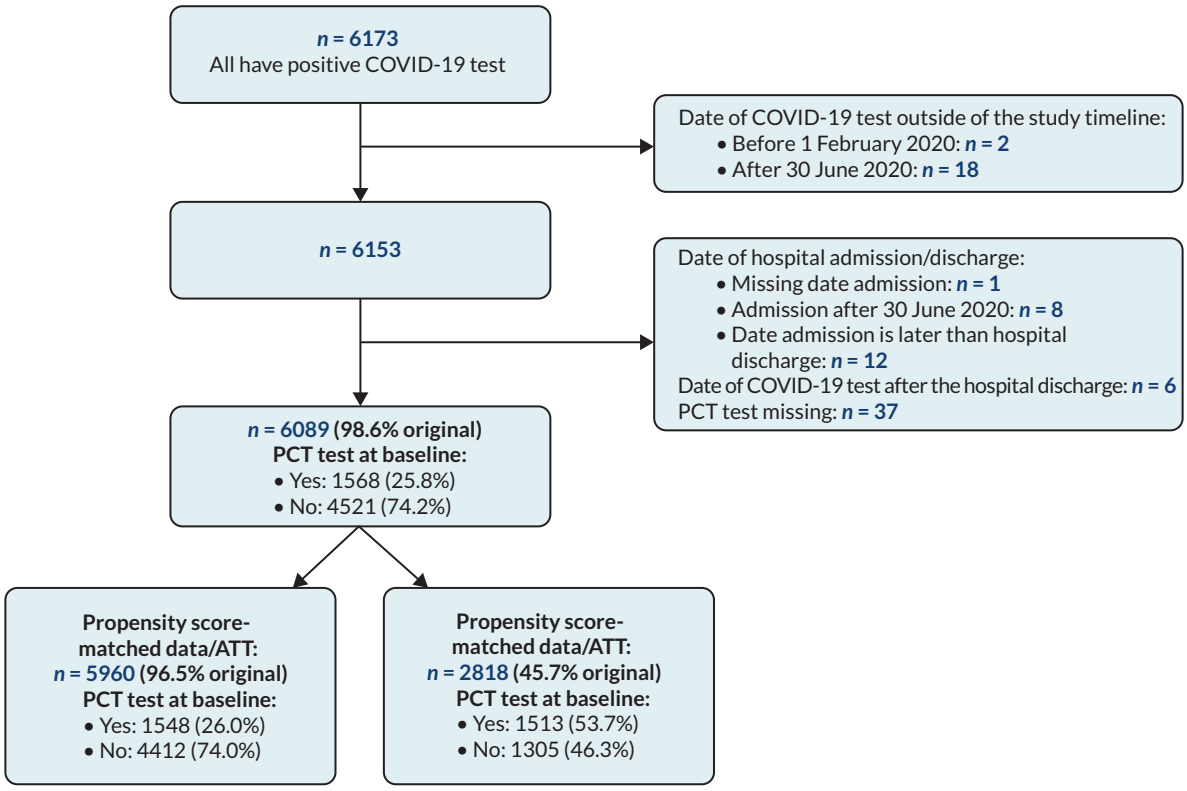

FIGURE 4 Recruitment flow chart and description of reasons for exclusions. Reproduced with permission from Sandoe *et al.*[18] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

TABLE 2 Patient characteristics for the whole sample set passing quality control (*n* = 6089)

	Frequency (%)
Age category (years)	
16–49	684 (11.2)
50–59	695 (11.4)
60–69	894 (14.7)
70–79	1427 (23.4)
> 80	2387 (39.2)
Unknown	2 (0.0)
Sex	
Female	2706 (44.4)
Male	3733 (55.4)
Unknown	10 (0.2)
Ethnicity	
White	4599 (77.2)
Mixed	47 (0.8)
Asian	247 (4.1)
Black	152 (2.5)
Other	246 (4.0)
Unknown	698 (11.5)
Smoking status	
No	2532 (41.6)
Yes	278 (4.6)
Ex-smoker	1587 (26.1)
Unknown	1692 (27.8)
ICU admission at baseline	
No	5634 (92.5)
Yes	399 (6.6)
Unknown	56 (0.9)
Has the patient died (as of when the data were collected and input in the study database)	
No	3375 (55.4)
Yes	2680 (44.0)
Unknown	34 (0.6)
Treatment: dexamethasone	
No	5826 (95.7)
Yes	230 (3.8)
Unknown	33 (0.5)

TABLE 2 Patient characteristics for the whole sample set passing quality control (*n* = 6089) (*continued*)

	Frequency (%)
Treatment: tocilizumab	
No	6056 (99.5)
Yes	6 (0.1)
Unknown	27 (0.4)
Treatment: remdesivir	
No	6009 (98.7)
Yes	50 (0.8)
Unknown	30 (0.5)

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and that there was no effect on resistant secondary bacterial infection. Conclusions were that baseline PCT testing was associated with a statistically significant reduction in antibiotic prescribing in hospitalised patients with COVID-19, indicating that PCT may have been an effective antimicrobial stewardship tool during the first wave of the pandemic. PCT testing appeared to be safe, having no measurable impact on mortality or LOS. Not all confounding factors could be accounted for, highlighting the need for adaptive, inclusive trials of infection diagnostics and effective implementation strategies to assess clinical utility, even in challenging circumstances, before routine introduction into clinical practice.

Limitations

The main limitations of the study were due to its retrospective, hospital record-based design with all the associated problems of missing data, incorrectly recorded information within the patient record and lack of randomisation. Missing data refer to the variables that were recorded in medical notes at participating hospitals and can be found in supplementary material from Llewelyn *et al*.[17] The percentage of missing data is reported for all variables (DDDs and activity data) separately for the English and Welsh data.

It was not practical to collect all the data pertaining for each case, for example collection of microbiology results was restricted to blood and respiratory samples only; and therefore, the rates of secondary bacterial infection and resistant infections may have been underestimated. It was also not possible to retrospectively assess the appropriateness of antibiotics according to local guidelines.

Work package 2.2: qualitative data and analysis

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The findings of this WP were published in *BMJ Open*.[19] The aim of this study was to explore the decision-making process around the use of antibiotics in the management of hospitalised patients with COVID-19 pneumonia during the first wave of the pandemic to identify the contextual factors, explore the feasibility and acceptability of PCT testing algorithms and identify the key ingredients of successful implementation and normalisation of PCT algorithms in the management of COVID-19.

The study was based on thematic analysis of semistructured interviews carried out with 29 clinicians from 6 of the NHS acute hospital trusts/health boards that took part in WP 2.1. The aim was to explore factors influencing the difference in antibiotic use between patients with COVID-19 pneumonia who did/did not have PCT testing at the

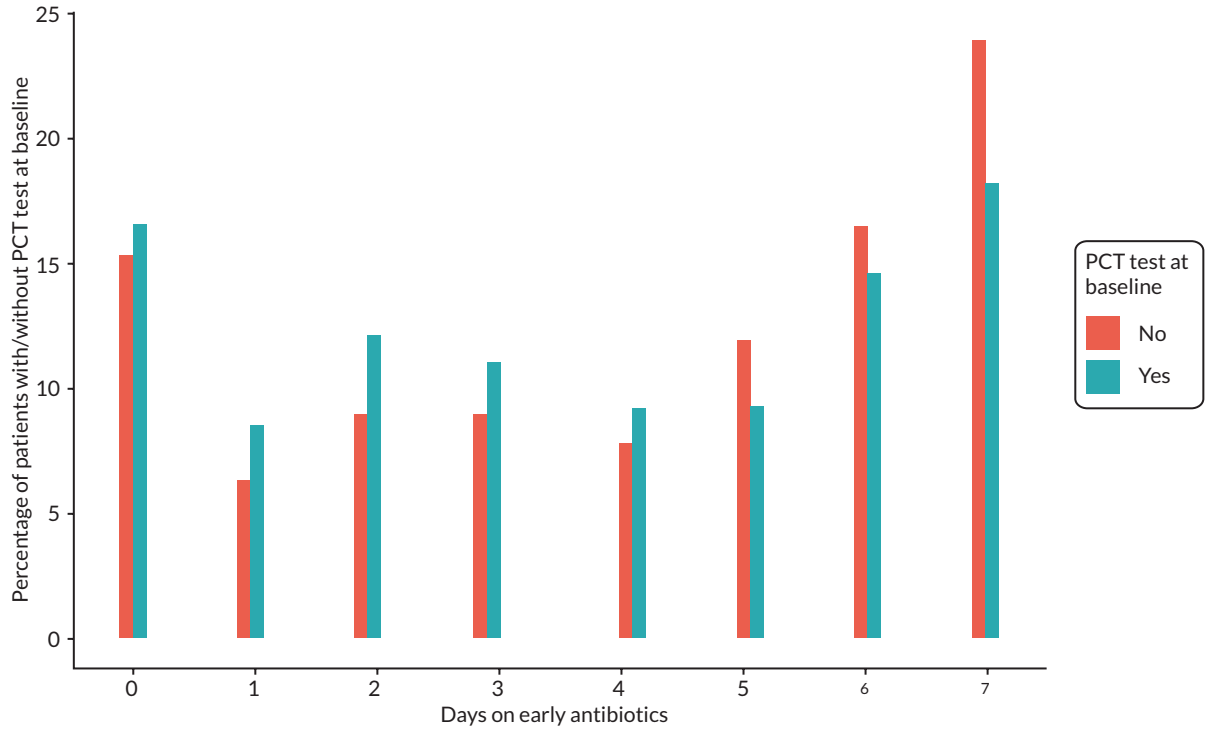

FIGURE 5 Histogram of days of primary outcome (early antibiotics, within first 7 days) according to whether a PCT test was done at baseline or not by using propensity score matching based on the ATT. Reproduced with permission from Sandoe *et al.*[18] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BT 4.0) licence, which permits others to distribute, remix, adapt and build up on this work, for commercial use, provided the original work is properly cited. See https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original.

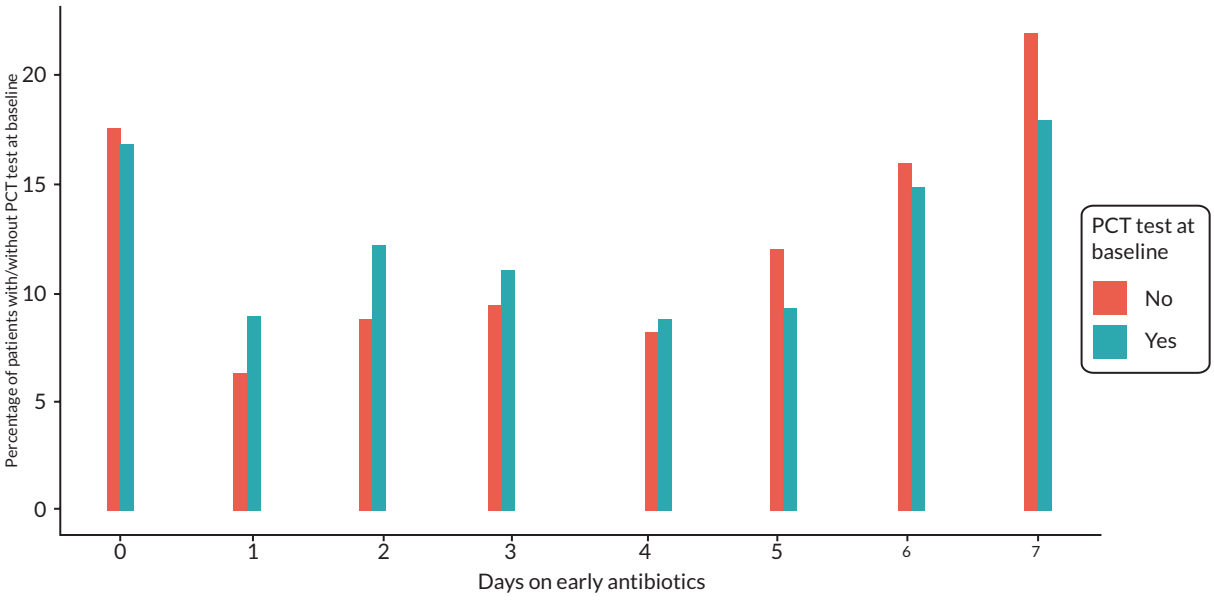

FIGURE 6 Histogram of days of primary outcome (early antibiotics, within first 7 days) according to whether a PCT test was done at baseline or not (n = 2818). Using propensity score matching based on the ATU. Reproduced with permission from Sandoe *et al.*[18] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BT 4.0) licence, which permits others to distribute, remix, adapt and build up on this work, for commercial use, provided the original work is properly cited. See https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original.

time of admission, and to explore the use of PCT testing, to guide antibiotic prescribing among patients who were hospitalised with COVID-19 during the first wave of the pandemic. The qualitative interviews with clinicians were designed to explore the decision-making process around the use of antibiotics in the management of patients with COVID-19 pneumonia. Six sites were selected based on whether they routinely used PCT testing before and during the pandemic; introduced PCT testing during the first wave of the pandemic or did not use PCT testing either before or during the first wave of the pandemic. Two sites from each category were selected.

It was found that the hospitals differed in their policies around the use of PCT due to the lack of direction in the national guidelines at the time, which left PCT use to local discretion. Participants for the interviews were sampled with maximum variation across (1) role (e.g. consultant/specialty trainee/nurse specialist/pharmacist, aiming to include at least one of each role from each site) and (2) hospital site (comparing sites that routinely used PCT, those that did not and those that introduced PCT during the first wave of the pandemic). The use of PCT and testing algorithms in guiding antibiotic decisions was explored, as well as the impact of the NICE COVID-19 rapid guideline on PCT use. A hypothetical scenario was presented to elicit factors influencing decision-making, including clinical and non-clinical influences. Analysis was thematic, seeking to identify common themes, patterns and meanings within the data. Following the generation of themes, a model of decision-making, using a matrix to represent the complexity of input into the decision, was proposed and refined within the team. The decision-making matrix was developed using the Eisenhower matrix as a base, including three variables: acuity, vulnerability and likelihood. The results show that during the first wave of the pandemic, recommendations to prescribe antibiotics for patients with COVID-19 pneumonia were based on concerns about secondary bacterial infections. However, as clinicians gained more experience with COVID-19, they reported the increasing confidence in their ability to distinguish between symptoms and signs caused by SARS-CoV-2 viral infection alone and secondary bacterial infections. Antibiotic prescribing decisions were influenced by factors such as clinician experience, confidence, senior support, situational factors and organisational influences (*Figure 7*). Conclusions were that the importance of clinician experience and of senior

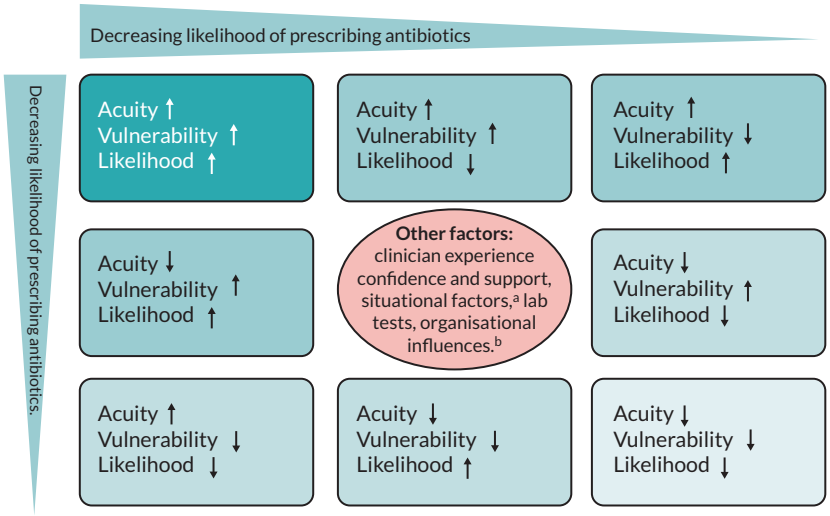

FIGURE 7 The complex factors which influenced decisions to prescribe antibiotics for patients with COVID-19. The blue boxes indicate the combination of factors contributing to the likelihood of prescribing antibiotics. The three main factors are: the acuity of the illness (how sick they are), the vulnerability of the patient to infection (age, immunosuppression, risk factors) and the likelihood of bacterial infection (based on clinical signs, laboratory tests and radiology). Other factors: clinician experience, confidence and support; situational factors; laboratory tests; organisational influences. The directional colour scale (orange) indicates the likelihood for prescribing antibiotics, with darker shaded areas weighted towards a higher likelihood of prescribing, and areas of lighter shading towards lower likelihood of prescribing. a, Situational factors include time of day, family/patient pressure to prescribe antibiotics, etc. (The question of how much impact family/patient pressure had on decision-making was presented to clinicians during the interviews. The majority expressed that they were senior and confident enough to ignore pressure to prescribe, which could be expressed during telephone calls from relatives. However, they might take patient wishes into consideration in terms of intolerances or preferences against particular antibiotics.); b, organisational factors include staffing levels, busyness of ED, availability of laboratory test results in real time, etc. Reproduced with permission from Henley *et al.*[19] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build up on this work, for commercial use, provided the original work is properly cited. See https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original.

review of prescribing decisions are important factors in optimising antibiotic stewardship. In addition, situational and organisational factors were identified, which could be optimised. The model presented in the study can be used as a tool to aid understanding of the complexity of the decision-making process around antibiotic prescribing and planning antimicrobial stewardship support in the context of a pandemic.

Limitations

One limitation of the qualitative study is that some interviews were conducted up to a year following the events, which may have resulted in recall bias. Interviewees expressed difficulty in remembering the details of the time period, which was characterised by chaos and uncertainty due to the emergence of a new disease. Another limitation is the exponential learning curve surrounding the disease, including how best to treat it and determine whether antibiotics were beneficial for a viral infection that presented similarly to sepsis. This rapidly evolving understanding of the disease may have impacted the accuracy of information provided by interviewees during the study.

Work package 2.3: integration and triangulation of data

The findings of this WP were submitted to *BMJ Open*. The aim was to integrate the results from the quantitative and qualitative data from four individual WPs of the PEACH study to evaluate the degree of agreement between different approaches used. A triangulation protocol was used to integrate the three quantitative data sources (survey, organisational-level data and patient-level data) and one qualitative data source (clinician interviews) collected for this study. Analysis of data sources took place independently, as described in relevant sections in this report, and key findings for each data source were then input into a matrix by a team member from each WP. A series of interactive discussion meetings took place with qualitative, quantitative, patient and public involvement (PPI) and clinical researchers, who worked together to group the key findings to produce statements relating to the study objective. Each statement and the key findings related to that statement were considered, and an assessment of whether there was agreement, partial agreement, dissonance or silence across all four data sources were made (convergence coding). The matrix was then interpreted to produce a narrative for each statement. The summary matrix can be seen in *Table 3*. For the full coding matrix, please refer to *Appendix 1*. Seven statements were produced relating to the PEACH study objective. There was agreement across all four data sources for our first key statement, 'During the first wave of the pandemic, PCT testing reduced antibiotic prescribing'. The second statement was related to this key statement, 'During the first wave of the pandemic, PCT testing safely reduced antibiotic prescribing'. Partial agreement was found between the quantitative patient-level data and qualitative clinician interviews. We have no data regarding safety from the quantitative survey and organisational-level data to contribute to this statement. For statements 3 and 4, 'PCT was not used as a central factor influencing antibiotic prescribing', and 'PCT testing reduced antibiotic prescribing in ED/AMU', there was agreement between organisational-level data and interviews with clinicians. The remaining two data sources' survey and patient-level data did not ask this question, so provided no data on this statement. For statement 5, 'PCT testing reduced antibiotic prescribing in ICU', there was disagreement between the organisational-level and patient-level data and data clinician interviews. The survey did not provide data on this statement. We therefore assigned dissonance to this statement. For statement 6, 'There were many barriers to implementing PCT testing during the first wave of COVID-19', there was partial agreement between the survey and clinician interviews, and no data were provided by the two remaining data sources (organisational-level data, and patient-level data). For statement 7, 'Local PCT guidelines/protocols were perceived to be valuable', only the clinician interviews provided data. The clinicians expressed that guidelines were valuable, but as there were no data from the other three data sources, we have assigned silence to this statement. Conclusions were that there was agreement between all four data sources on our key finding 'During the first wave of the pandemic, PCT testing reduced antibiotic prescribing'. Data, methodological and investigator triangulation and a transparent triangulation protocol give validity to this finding.

Limitations

Triangulation can be a complex process, and there are a variety of possible approaches to integrate qualitative and quantitative data.[20] We used a triangulation protocol to integrate the qualitative and quantitative data for PEACH in a transparent and systematic way. There is a risk of bias in the process, but this was limited by using a transparent and questioning methodology. The PEACH research team has a broad range of expertise and includes non-clinicians and clinicians, including those who are sceptical about the value of PCT, but they all have equipoise and would be willing to recruit into clinical trials.

Work stream 3: health economic evaluation

Some text in this section has been reproduced from Webb *et al*.[21] and Webb *et al*.[22] These are Open Access

TABLE 3 Summary table of triangulation coding matrix for the PEACH study of the impact of PCT testing on antibiotic prescribing during the COVID-19 pandemic

	Statement	Data source 1: survey (Quan)	Data source 2: organisational-level data (Quan)	Data source 3: patient-level data (Quan)	Data source 4: interviews (Qual)	Convergence coding
1	During the first wave of the pandemic, PCT testing reduced antibiotic prescribing	Agree	Agree	Agree	Agree	Agreement
2	During the first wave of the pandemic, PCT testing safely reduced antibiotic prescribing	No data	No data	Agree	Partial agreement	Partial agreement
3	PCT was not used as a central factor influencing antibiotic prescribing	No data	Agree	No data	Agree	Agreement
4	PCT testing reduced antibiotic prescribing in ED/AMU	No data	Agree	No data	Agree	Agreement
5	PCT testing reduced antibiotic prescribing in ICU	No data	Disagree	Disagree	Agree	Dissonance
6	There were many barriers to implementing PCT testing during the first wave of COVID-19	Partial agreement	No data	No data	Agree	Partial agreement
7	Local PCT guidelines/protocols were perceived to be valuable	No data	No data	No data	Agree	Silence

This synopsis should be referenced as follows: Euden J, Albur M, Bestwick R, Bond S, Brookes-Howell L, Dark P, *et al.* Procalcitonin evaluation of antibiotic use in COVID-19 hospitalised patients: The PEACH mixed methods study. *Health Technol Assess* 2025;**29**(52):1–32. https://doi.org/10.3310/GGFF9393

The objectives of the health economic evaluation were to: (1) identify and review published evidence of cost-effectiveness, (2) estimate the patient-level cost of illness from COVID-19 in NHS Trusts that used PCT versus those that did not and (3) determine the cost-effectiveness of PCT testing to guide antibiotic decisions in individuals hospitalised with COVID-19.

Work package 3.1: identifying and reviewing published evidence of cost-effectiveness

Two scoping reviews were conducted using pre-defined search terms and inclusion and exclusion criteria; that is, a systematic search strategy. The aim of the first review was to identify economic evaluations of the cost-effectiveness of PCT to guide decisions about whether to prescribe antibiotics or other treatment. The aim of the second review was to provide an overview of studies reporting the quality of life (QoL) data for individuals who were hospitalised with COVID-19 and the methods used to collect these data.

For the first review of PCT cost-effectiveness studies, 49 studies were selected for data extraction. One systematic review of systematic reviews was identified; five individual systematic reviews and one meta-analysis were identified. The remaining studies were mostly full economic evaluations; that is, they compared costs and health outcomes (n = 11), observational studies (retrospective and prospective) (n = 11) and RCTs, which only compared costs (n = 6). A large proportion (n = 22) of the included studies focused on the cost-effectiveness of PCT in individuals with sepsis or suspected sepsis. Other common target conditions were acute respiratory infection (n = 7) and pneumonia (n = 5). Although this scoping review was useful for the purposes of informing our subsequent cost-effectiveness analysis, given the number of systematic reviews identified, this review was not written up for publication.

The second review of studies reporting QoL data for individuals who were hospitalised with COVID-19 was published in NIHR *HTA*.[21] A total of 35 papers were selected for data extraction (*Figure 8*). The most common study types were economic evaluations (N = 13), followed by cross-sectional studies (N = 10) (*Figure 9*). All of the economic evaluations used published utility values for other conditions to represent COVID-19 inpatients' QoL. The most popular QoL survey measure was the Pittsburgh Sleep Quality Index (N = 8). There were 12 studies that used a mental health-related survey and 12 that used a sleep-related survey. Five studies used EuroQol-5 Dimensions (EQ-5D), but only one collected responses from people in the acute phase of COVID-19. Studies reported a general negative impact on QoL for people hospitalised with COVID-19, although many studies did not include a formal comparison group. QoL data were collected from people hospitalised with COVID-19 relatively early in the pandemic; however, there was a lack of consensus as to what survey measures to use, and few studies used generic health measures. *Figure 10* shows the frequency of using different QoL measures. Economic evaluations for COVID-19 treatments typically did not use utilities collected from people with COVID-19.

Limitations

Although these reviews were based on systematic searches, the reviews were not conducted as full systematic reviews. For the review of studies reporting QoL data for individuals who were hospitalised with COVID-19, the latest date for which any included study was open for data collection was September 2021. COVID-19 has evolved during and since the pandemic, and widespread vaccination has reduced the probability of serious illness for those infected. Thus, there may be limitations in the applicability of the QoL data identified in this review to individuals hospitalised with COVID-19 currently and in the future. Another limitation to the extracted data is that it was often difficult to distinguish between people hospitalised due to COVID-19 and those hospitalised for another reason but who also had COVID-19.

Work package 3.2: patient-level cost of illness from COVID-19 in National Health Service Trusts that use procalcitonin versus those that did not

The findings from this WP were embedded within a paper, which also included the results from WP 3.3 and were published in the *Journal of Antimicrobial Chemotherapy*.[22]

Using the patient-level data from WP 2.1, a propensity score-matched analysis balanced the distributions of important confounders between groups of inpatients whose PCT was and was not tested at baseline. The daily cost of a general ward and ICU stay was obtained, along with the average unit price for a PCT test. To calculate the

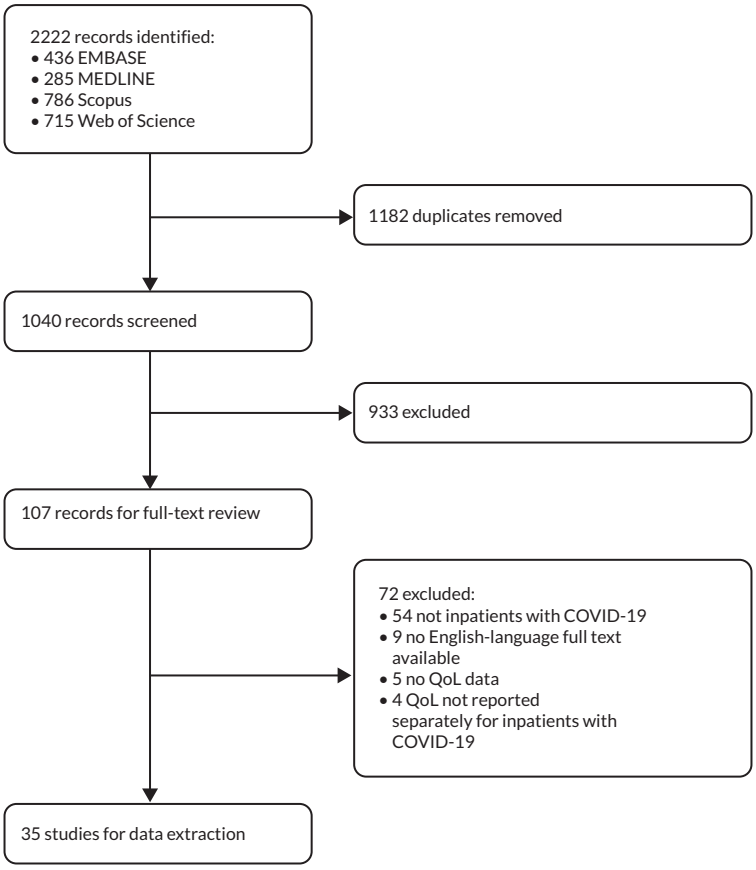

FIGURE 8 Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram. Reproduced with permission from Webb *et al.*[21] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build up on this work, for commercial use, provided the original work is properly cited. See https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original.

cost of antibiotics in this study, data on the name, dose and frequency of dose for antibiotics were collected. These data were interpreted with the assistance of a clinician. As per NICE guidelines, medication was preferentially matched to a cost provided in the drugs and pharmaceutical electronic Market Information Tool and, where this was not possible, to NHS indicative prices provided by NICE *British National Formulary* records. A per-dose cost representing the cost of antimicrobial resistance (AMR) was estimated, based on a previously published method.

The total cost was lower overall when people had a PCT test performed at baseline versus those that did not (£9830 vs. £10,700) (see *Table 3*). This result was the case both in the short (1 year post admission) and long term (lifetime analysis). In terms of the distribution of costs, there was a long tail, with 90% of patients' costs < £15,000, but a smaller subset of 50 patients who had costs in excess of £100,000. The very highest individual cost was over £200,000. The long tail in the distribution of costs was largely due to some patients having long general ward and ICU stays.

Limitations

As an observational study, there is a possibility that there were some unknown confounding factors which could not be adjusted for in the matched analysis. A sensitivity analysis conducted as part of the main statistical analysis indicated that this is a possibility and therefore could have influenced the estimates that underpinned this costing analysis. The difference in total costs estimated for those who had PCT at baseline and those who did not was heavily driven by a subset of individuals who had long hospital stays. Although this difference reflects what was observed in the large data set obtained, this dependency on a small subset of individuals means that there is considerable uncertain around this result.

Work package 3.3: cost-effectiveness of procalcitonin testing to guide antibiotic decisions in individuals hospitalised with COVID-19

The results from this WP were published in the *Journal of Antimicrobial Chemotherapy*.[22] A health economic model was created using a decision tree to represent 1 year post admission and a Markov model to represent the rest of

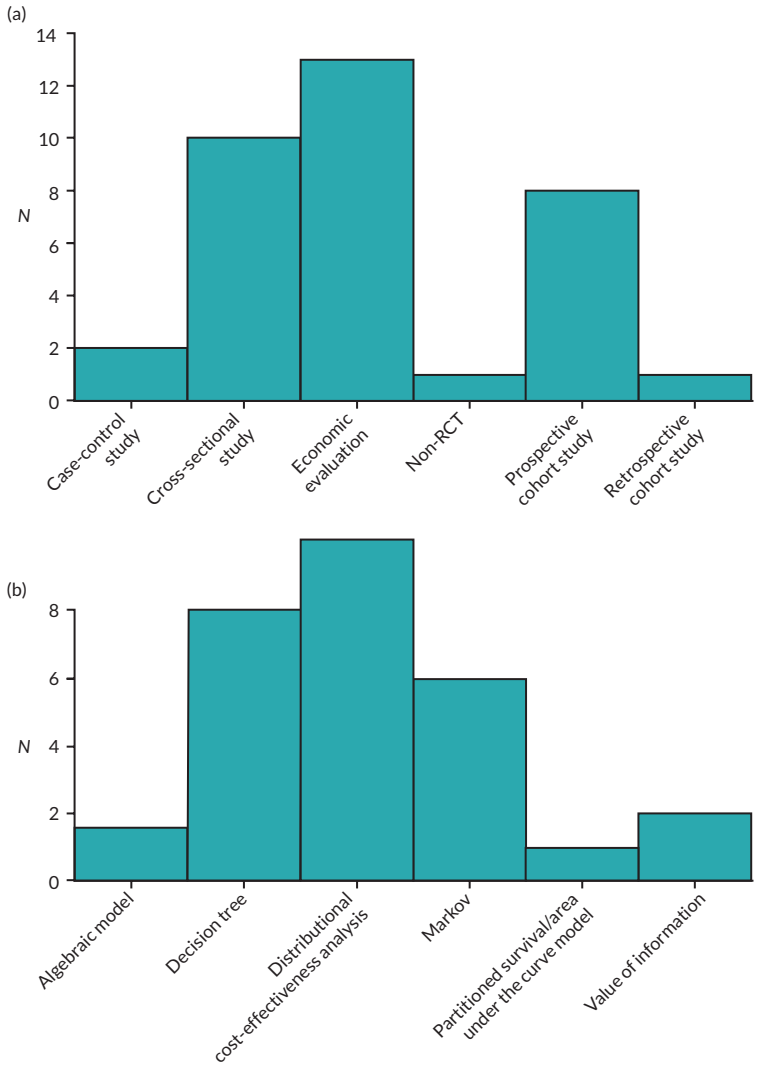

FIGURE 9 (a) Frequency of using study design; (b) frequency that economic evaluation studies used different modelling approaches. Reproduced with permission from Webb *et al.*[21] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build up on this work, for commercial use, provided the original work is properly cited. See https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original.

patients' lives (*Figure 11*). The costing analysis conducted as part of WP 3.2 was embedded in the model, and health-related QoL estimates were obtained from the literature. The model was used to estimate costs and quality-adjusted life-years (QALYs) for baseline PCT versus no baseline PCT. In line with the NICE reference case, cost-effectiveness was based on a £20,000/QALY threshold (*Table 4*). On average, people who had a PCT test at baseline had shorter general ward and ICU stays and spent less time on antibiotics (although there was considerable overlap in 95% CIs). The biggest QALY losses and costs were associated with general ward and ICU days. Those who had a PCT test at baseline accrued more QALYs (8.76 vs. 8.62). As those who had a baseline PCT also had lower total costs, the overall incremental cost-effectiveness ratio (ICER) indicated that baseline PCT testing was dominant over no baseline PCT testing. It is important to note that there is considerable uncertainty around this result; the probability of cost-effectiveness was 0.579 when considering a 1-year time horizon and was 0.872 when considering a lifetime horizon. The results suggest that using PCT to guide antibiotic therapy in patients hospitalised with COVID-19 is more likely to be cost-effective than not, albeit with considerable uncertainty.

Limitations

As this was an analysis which was largely based on matched retrospective observational data, QoL data were not available from the individuals in the study and therefore estimates had to obtained from the literature for this component of the model. As described in WP 3.1, the quality of the health-related QoL data for

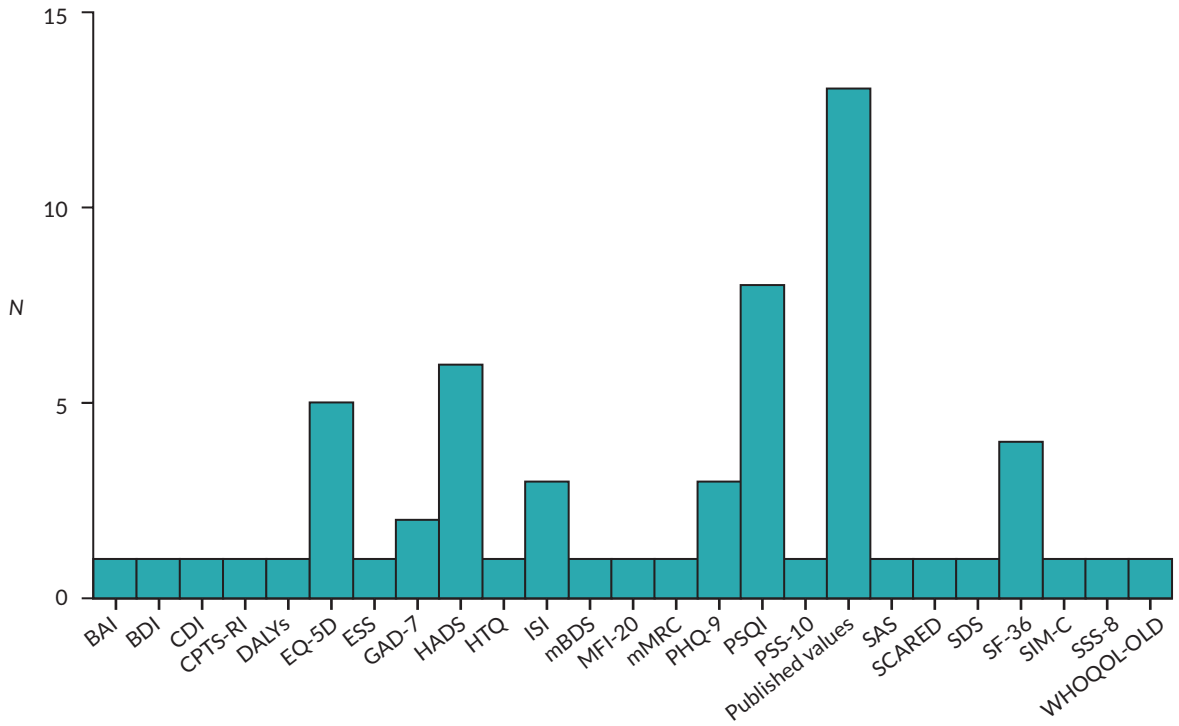

FIGURE 10 Frequency of using different QoL measures. BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CDI, Child Depression Inventory; CPTS-RI, Child Post-Traumatic Stress Reaction Index; DALY, disability-adjusted life-year; ESS, Epworth Sleepiness Scale; GAD-7, Generalised Anxiety Disorder-7; HADS, Hospital Anxiety and Depression Scale; HTQ, Harvard Trauma Questionnaire; ISI, Insomnia Severity Index; mBDS, modified Borg Dyspnea Scale; MFI-20, Multidimensional Fatigue Inventory; mMRC, modified Medical Research Council Dyspnea Scale; PHQ-9, Patient Health Questionnaire-9 items; PSQI, Pittsburgh Sleep Quality Index; PSS-10, Perceived Stress Scale; SAS, Self-rating Anxiety Scale; SCARED, Screen for Child Anxiety Related Disorders; SDS, Self-rating Depression Scale; SF-36, Short Form questionnaire-36 items; SIM-C, Short Inventory of Mindfulness Capability; SSS-8, 8-item Somatic Symptom Scale; WHOQOL-OLD, World Health Organization Quality of Life Instrument – Older Adults Module. Reproduced with permission from Webb *et al.*[21] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build up on this work, for commercial use, provided the original work is properly cited. See https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original.

individuals hospitalised with COVID-19 was unclear in terms of whether it reflected individuals hospitalised because of COVID-19, or whether it included individuals hospitalised for other reasons but who also had COVID-19. The same limitation described for WP 3.2, relating to the observational nature of the underlying analysis, also applies to this analysis and it is possible that some of the differences observed could be influenced by unknown confounding factors.

Patient and public involvement

Aim

The role of the PPI group for the PEACH study was to advise on the design, analysis and reporting of the study and to ensure that the study team were processing confidential data in an appropriate manner and in accordance with our ethical approvals.

Methods

Together with the research team, the PPI group coproduced the grant preparation through to dissemination. This study arose from a commissioned call from the NIHR to better understand and manage the health and social care consequences of the global COVID-19 pandemic. The PPI group included members of the public with lived experience of COVID-19, either as a patient or a carer, and who could guide the design and content of dissemination activities. The lead PPI coinvestigator was also included in our qualitative WS analysis.

Results of public and patient involvement input

The PPI members attended monthly study management group meetings and advised on many issues that arose during the study and were fully involved and contributed to the advice and decisions made during these meetings.

As the main PEACH study did not involve patient recruitment, the PPI members led on engagement with patient groups and the wider public through their involvement as members of ICUsteps, Antibiotic Action (a public awareness group of the British Society for Antimicrobial Chemotherapy) and Antibiotic Research UK to publicise

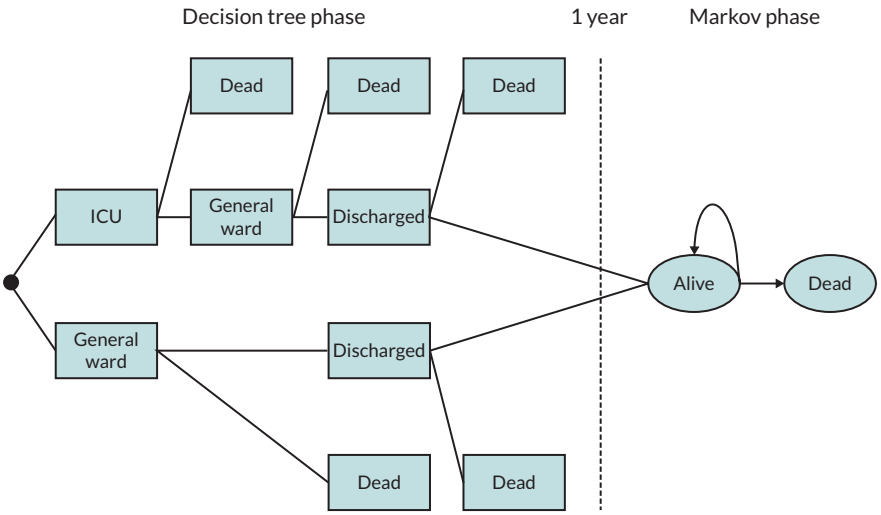

FIGURE 11 Economic evaluation model. Patients who did and did not receive a PCT test followed the same pathway. Reproduced with permission from Webb *et al.*[22] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

TABLE 4 Survival time, total QALYs and costs for patients who had a PCT performed at baseline and those who did not

	Baseline PCT		No baseline PCT	
	Mean	**95% CI**	**Mean**	**95% CI**
Survival time (days)	234	(227 to 241)	232	(222 to 241)
Probability of 1-year survival	0.615	(0.596 to 0.634)	0.605	(0.578 to 0.630)
Baseline utility	0.767	(0.765 to 0.769)	0.769	(0.766 to 0.772)
Total QALYs (decision tree phase only)	0.486	(0.472 to 0.501)	0.479	(0.460 to 0.498)
Total QALYs (decision tree and Markov phases)	8.76	(8.44 to 9.09)	8.62	(8.15 to 9.08)
Total cost (£)	9830	(9040 to 10,600)	10,700	(8830 to 12,300)
ICER (decision tree phase only)			−117,000	(−1,300,000 to 1,180,000)
ICER (decision tree and Markov phases)			−5930	(−58,300 to 55,300)

Source
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the study through these channels. The PPI members also authored and produced articles for public dissemination (blogs and poems) to highlight the research.

Equality, diversity and inclusion

In total, this study obtained a large sample of patient data from a geographical range of 11 hospitals/health boards across England and Wales, and a range of hospital types, including teaching and district general hospitals, in order to improve generalisability. The sampling strategy was purposeful and deliberately included institutions that did/did not introduce/use PCT testing during the first wave of the COVID-19 pandemic. Data were collected for 6173 individuals who fulfilled the eligibility criteria. After data cleaning and quality control, 6089 patients remained, of whom 97.9% were used for propensity score matching. Ethnicity data and other patient characteristics from the entire data set were obtained ahead of propensity score matching. A total of 77.2% of patients were White, 0.8 were mixed ethnicity, 4.1% were Asian, 2.5% were Black,

4% were another ethnicity and, for 11.5%, the ethnicity was not known. A total of 44.4% were females, and 55.4% were males (0.2% were unknown). Representation across all age groupings was good, with 11.2% aged 16–49 years, 11.4% aged 50–59 years, 14.7% aged 60–69 years, 23.4% aged 70–79 years and 39.2% aged over 80 years (see *Table 4*).

Impact and learning

The study results were planned to inform the planning of future waves of the pandemic, but due to delays in ethical approval, data collection and analysis, the pandemic had been declared over by the time results were finalised. However, patients continue to be admitted to hospital with COVID-19.

1. During the first wave of the pandemic, clinicians had to manage patients suffering from a new severe illness and diagnostic uncertainty was a major problem. Practice changed rapidly during this period, which was reflected by the highly variable rates of antibiotic prescribing we observed in this period. Thus, we were studying a time period characterised by rapid change. The controlled interrupted time series analysis allowed for this period to be studied and, although organisational-level data were used, the findings were similar to those of the patient-level data analysis. Learning from this aspect is that quasi-experimental approaches can provide useful data when it is impractical to undertake trials.
2. Collection of retrospective routine hospital data is challenging and would be facilitated by anonymised data being received from NHS Digital or another secure platform for analysis. Many of the variables collected are not currently collected by NHS Digital (e.g. blood test results, microbiology results and antibiotic prescribing data) but exist on the electronic patient record. There needs to be public awareness campaigns targeted at individuals and communities to allow the normalisation of the use of anonymised routinely collected data in peer-reviewed studies so that these data can be used to optimise individual care and maximise broader societal benefit.
3. The collection of routine data from hospital paper records was time-consuming, taking on average up to 3 hours per patient. In some hospitals with electronic health record systems, data collection was much quicker (down to half an hour per patient). Not all electronic health record systems were easy to use; those that uploaded scans of paper forms were particularly difficult to use.
4. There are no standardised definitions of antimicrobial-resistant infections to use as outcome measures. Until such definitions exist, it will be challenging to compare studies.
5. Propensity score matching is a useful tool for analysing retrospectively collected data and enabling research using real-world data, but not all variables can be matched (including significant variables which are either not collected or not included in the matching). RCTs which do not exclude at-risk groups will provide the most reliable evidence on the effectiveness of an intervention.
6. The triangulation process for integration of the qualitative and quantitative data was conducted using published methods,[23] which improves transparency and provides additional insight into the study findings.

Impact

- The ADAPT-sepsis trial[24] reported that in adults (≥ 18 years), in ICUs, requiring critical care within 24 hours of initiating intravenous antibiotics for suspected sepsis, care guided by measurement of PCT reduces antibiotic duration safely compared with standard care, but C-reactive protein does not.
- In the BATCH trial of hospitalised children with suspected or confirmed bacterial infection, the introduction of a PCT-guided algorithm did not reduce the duration of intravenous antibiotics treatment and it is non-inferior to usual care for safety outcomes.[25]
- Until publication of trial data from the PRONTO trial, baseline PCT testing could reasonably be used to aid antibiotic prescribing decisions in patients in EDs and AMUs with suspected COVID-19; it reduced antibiotic use without evidence of harm and was likely to be cost-effective.
- PEACH found some evidence from our qualitative WP that PCT testing was beneficial for use in ICU patients, but this was not supported by quantitative analyses, so guidance and evidence for PCT use in this setting may need to be reviewed.
- From the retrospective data, use of multiple PCT tests was associated with an increased antibiotic use.

Implications for decision-makers

Procalcitonin testing was introduced during the pandemic in a non-standardised way; in spite of this, it was associated with reduced antibiotic use. No harms in terms of mortality or LOS were identified. More implementation research is needed to optimise PCT use, and better trial infrastructure is needed to ensure that tests are safe and effective before introduction.

- Until publication of data from all three PCT trials, baseline PCT testing could reasonably be used to aid

antibiotic prescribing decisions in patients in EDs and AMUs with suspected COVID-19; it reduced antibiotic use without evidence of harm and was most likely to be cost-effective.
- National guidelines and algorithms on how to use PCT (cut-off and actions to be taken) are needed to standardise practice.
- Implementation strategies need to be used beyond simply making PCT testing available.

Research recommendations

Further analysis of the PEACH data could look in more detail at PCT and antibiotic use in the ICU setting.

The relationship between different inflammatory markers and their effect on antibiotic use could be explored in the PEACH data.

Adaptive platform trials embedded in routine clinical care are needed to comprehensively evaluate multiple diagnostic tests and to robustly and rapidly establish clinical utility, safety, cost-effectiveness and implementation outcomes in reducing antibiotic use.

Conclusion

Baseline PCT testing was associated with a statistically significant reduction in antibiotic prescribing in hospitalised patients with COVID-19, so PCT appears to have supported antimicrobial stewardship during the first wave of the pandemic. There was no impact on mortality or hospital/ICU LOS, or resistant secondary bacterial infections. This work highlights the need for adaptive, inclusive, wide-reaching trials of infection diagnostics to assess clinical utility before routine introduction into clinical practice.

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that those are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

Patient data were collected under the 'COPI Notice' issued under Regulation 3(4) and the corresponding transition to Section 5 of the Health Service (Control of Patient Information) Regulations 2002 to allow processing of confidential patient information without consent.

Data-sharing statement

The statistical analysis plan has been published and is publicly available as supplementary information to the PEACH protocol paper (https://doi.org/10.3390/mps5060095). The underlying data set is not publicly available for ethical and legal reasons. Within the remits of Condition 1 of the Health Service Regulations, sensitive information cannot be shared. All data releases are subject to application, assessment and approval. Requests for access to relevant anonymised data should be submitted to the Centre for Trials Research at PEACH@cardiff.ac.uk.

Ethics statement

This study was approved by the West Midlands – Solihull Research Ethics Committee on the 3 March 2021 (REC Reference 21/WM/0052).

Information governance statement

Cardiff University is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, Cardiff University is the Data Processor; University of Leeds is the Data Controller, and personal data were processed in accordance with their instructions.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GGFF9393.

Primary conflicts of interest: Mahableshwar Albur has had contracts from HR UK. The Showering Fund, David Telling Trust, Southmead Hospital Charities, Royal Society of Medicine and Pfizer, has received consulting fees from Pfizer, Merck and Shionogi and has received honoraria payments and equipment from Pfizer. Lucy Brookes-Howell is co-lead of Qualitative Research in Trials Group [subgroup of the Trials Methodology Research Partnership's (TMRP's) Trial Conduct working group]. Paul Dark is chief investigator of the ADAPT-Sepsis study (NIHR128374) investigating biomarker-guided antibiotic treatment decisions in adult patients with sepsis, and NIHR HTA funding payments were made to his employing institution. He is also the Deputy Medical Director, NIHR Research Delivery Network, Leeds and London, and he receives funding to his employer through a secondment with the University of Leeds. Sarah Gerver is a principal investigator and received a grant from BSAC on use of immunomodulatory therapy and/or antimicrobials and their association with secondary infections amongst hospitalised patients with COVID-19, and she receives payment to her institution. Ryan Hamilton has received a research grant from Antibiotic Research UK and received consulting fees from A Menarini. Thomas Hellyer has received NIHR EME funding (128374) and NIHR HTA funding (134101) and is a NIHR HTA committee member (General board from November 2022 to November 2023) and Clinical Evaluation and Trials (August 2024–current). Susan Hopkins has received grants from the NIHR (NIHR132254, NIHR200915), UKRI (MR/W02067X/1, MR/X009297/1 and MR/V03488X/1), and she has received travel expenses for speaking at the ESCMID Global Conference and is the UK Health Security Agency Executive. Daniel Howdon has received funding for the PEACH study (NIHR132254) payments to his institution for ESRC grants, has received consulting fees for Organisation for Economic Co-operation and Development and United Nations Asia-Pacific Region and has received payments to his institution from University of Lucerne. Martin Llewelyn has received NIHR grants for the following projects: PEACH (NIHR132254), ARK digitally Enabled Sustainable Implementation (NIHR206517), Staphylococcus aureus Network Adaptive Platform (SNAP Trial – NIHR133719) and Duration of antibiotic treatment in urinary tract infection (DurATIon-UTI Trial – NIHR134854) and has received ESRC funding for Optimising COVID-19 Testing System (OCTS). He is also an IDMC member of the NIHR funded SHORTER trial (NIHR134101). Wakunyambo Maboshe has received funding from NIHR HTA programme for PRONTO trial (NIHR17/136/13). Iain McCullagh is a member of the DSMB for the SPACE trial (NIHR129069). Philip Pallmann has received NIHR HTA funding for contribution to the PRONTO trial (NIHR17/136/13), BATCH trial (NIHR15/188/42) and as a co-chief investigator for the PROTECT project (NIHR156664), Medical Research Council (MRC)-NIHR EME funding for contribution to the PRECISE study (NIHR129960) and is a member of the EME Funding Committee. David Partridge is the President of the British Infection Association. Neil Powell had received honoraria payments from Thermo Fisher for lectures. Colin Richman is the company director of RX-Info Ltd. Tamaz Szakmany has received NIHR HTA funding (NIHR132254, NIHR151601 and NIHR131784), has received honoraria payments from Thermo Fisher, owns the patent for EP3519594B1, is a trustee for Intensive Care National Audit and Research Centre, is editor-in-chief, Critical Care Explorations, and is associate editor, Journal of Intensive Care Society. Stacy Todd is co-chief investigator for NIHR HTA Grant PRONTO (2019–present, Award 17/136/13) and co-applicant for an INNOVATE UK grant – Self-sanitising coatings to reduce healthcare associated infections (project reference 10026942). Robert West declares the following interests: HS&DR Researcher-Led Panel Members, PHR – Research Funding Board and HS&DR Funding Committee. Enitan Carrol has received funding for the PEACH study (NIHR132254), BATCH trial (NIHR15/188/42) and PROTECT project (NIHR156664); Medical Research Council (MRC)-NIHR EME funding for the PRECISE study (NIHR129960) and is a member of the HTA Commissioning Funding Committee. Jonathan Sandoe has received NIHR HTA funding for the PEACH study (NIHR132254), NIHR-PGFAR grant funding for ALABAMA (RP-PG-1214-20007), NIHR Invention for Innovation grant for PALOH (II-LB-0417-20002), grants from ESRC and MRC, received personal payments from Tillots pharma and Medtronic, has a small molecule measurement patent planned and is a member of the Project Advisory Board for the NIHR Invention for Innovation funded PALOH study (II-LB-0417-20002). All other authors declare no competing interests.

Department of Health and Social Care disclaimer

This publication presents independent research commissioned by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication

are those of the authors and do not necessarily reflect those of the NHS, the NIHR, MRC, NIHR Coordinating Centre, the Health Technology Assessment programme or the Department of Health and Social Care.

This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Publications

Llewelyn MJ, Grozeva D, Howard P, Euden J, Gerver SM, Hope R, *et al*. 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. *J Antimicrob Chemother* 2022;**77**:1189–96. https://doi.org/10.1093/jac/dkac017

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Study registration

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This synopsis provided an overview of the research award *Procalcitonin: Evaluation of Antibiotic use in COVID-19 Hospitalised patients. (PEACH)*. For other articles from this thread and for more information about this research, please view the award page (www.fundingawards.nihr.ac.uk/award/NIHR132254).

About this synopsis

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List of abbreviations

AMU	acute medical unit
ATT	average effect of testing on the tested
ATU	average effect of testing on the untested
CAP	community-acquired pneumonia
DDD	defined daily doses
ED	emergency department
EQ-5D	EuroQol-5 Dimensions
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
LOS	length of stay
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PCT	procalcitonin
PEACH	Procalcitonin Evaluation of Antibiotic use in COVID-19 Hospitalised patients
PPI	patient and public involvement
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization
WP	work package
WS	work stream

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Appendix 1 PEACH coding matrix

PEACH coding matrix					
	Findings from WSs				
Statement	Data source 1: survey (WP 1.1)	Data source 2: organisational-level data (WP 1.2)	Data source 3: patient-level data (WP 2.1)	Data source 4: qualitative interviews (WP 2.2)	Convergence coding
1: During the first wave of the pandemic, PCT testing reduced antibiotic prescribing	Agree: Perceived value of PCT by the majority of respondents 78/114 (68.4%)	Agree: ED/AMU: Introduction of PCT in EDs/acute medical admission units was associated with an initial statistically significant decrease in the total antibiotic use of −1.08 (95% CI −1.81 to −0.36) DDDs of antibiotic per admission per week per trust	Agree: PCT use was associated with reduced days of early antibiotics (within first 7 days of a positive COVID-19 test) and total days of antibiotic treatment	Agree: Clinicians in hospitals where PCT was used previously or introduced during the first wave of the pandemic reported that the PCT test contributed to decision-making about antibiotic prescribing. They predicted that unnecessary antibiotic doses would have been reduced where the test was carried out. The stopping of antibiotics early was attributed to PCT results	Agreement
2: During the first wave of the pandemic, PCT testing safely reduced antibiotic prescribing	No data	No data	Agree: PCT testing was not associated with increased 30- or 60-day mortality and was not associated with an increase in hospital or ICU LOS	Partial agreement: Most clinicians were positive about the use of PCT in guiding them to make antibiotic prescribing decisions. There was a divide between the majority who made the judgement that PCT had contributed safely to the reduction of antibiotic use within their hospital, and a minority who were more circumspect and would prefer to see evidence for the efficacy of PCT before it was used widely	Partial agreement
3: PCT was not used as a central factor influencing antibiotic prescribing	No data	Agree: Although there was an initial significant drop in organisational prescribing, this declined over time. This effect was subsequently lost at a rate of 0.05 (95% CI 0.02 to 0.08) DDDs per admission per week per trust. Similar effects were found for first-line antibiotics prescribed for CAP and for analysis restricted to COVID-19 admissions	No data	Agree: During the first wave, there was a lot of confusion and rapidly changing advice around tests and treatments. Some clinicians reported that the tests contributed very little to the decision-making around antibiotic prescriptions, as these decisions were based on clinical judgement	Agreement

continued

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Statement	Findings from WSs				Convergence coding
	Data source 1: survey (WP 1.1)	Data source 2: organisational-level data (WP 1.2)	Data source 3: patient-level data (WP 2.1)	Data source 4: qualitative interviews (WP 2.2)	
4: PCT testing reduced antibiotic prescribing in ED/AMU	No data	Agree: Introduction of PCT in EDs/acute medical admission units (ED/AMU) was associated with an initial statistically significant decrease in total antibiotic use	No data	Agree: Clinicians in EDs found that PCT use was more widespread than in other parts of the hospital. There was a heightened anxiety around the unknown infection at the beginning of the pandemic. This led to a need for more evidence for clinicians to be reassured in stopping antibiotics. Clinicians saw their role as providing evidence for de-escalation. PCT was seen as a useful tool for providing this evidence	Agreement
5: PCT testing reduced antibiotic prescribing in ICU	No data	Disagree: In ICU settings, PCT was not associated with any significant change in antibiotic use	Disagree: There was no statistically significant association between antibiotic prescribing in patients admitted early to ICU and baseline PCT testing	Agree: Clinicians spoke about how PCT was used for reassurance purposes in ICU. As with ED, it was considered as a useful tool to enable reduction of antibiotic use	Dissonance
6: There were many barriers to implementing PCT testing during the first wave of COVID-19	Partial agreement: 55 of 114 (48%) of respondents reported that their organisation had a guideline for PCT use	No data	No data	Agree: During the first wave of the pandemic, clinicians reported a lot of confusion and rapidly changing advice and guidelines around tests and treatments, meaning that guidelines were not always followed. There was therefore chaotic implementation of PCT testing, with some clinicians being aware of guidelines and others not, and with guidelines being followed differently in different parts of the hospital	Partial agreement
7: Local PCT guidelines/protocols were perceived to be valuable	No data	No data	No data	Agree: Clinicians who reported using the available guidelines said that they were helpful, especially due to COVID being a new condition. This was particularly when the guidelines were very clear in the parameters, and when they were readily available to access	Silence