Doxycycline for suspected COVID-19 in people at high risk in the community: results from PRINCIPLE, the UK randomised, controlled, open-label adaptive platform trial

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Summary (345 words)

Background
Doxycycline is often used for COVID-19 respiratory symptoms in the community despite lack of evidence from clinical trials. We aimed to assess the effectiveness of doxycycline to treat suspected COVID-19 in the community among people at higher risk of adverse outcomes.

Methods
We conducted the UK national, primary care, open-label, multi-arm, adaptive Platform Randomised trial of INterventions against COVID-19 In older peoPLE (PRINCIPLE). People aged ≥65 years, or ≥50 years with comorbidities, and unwell ≤14 days with suspected COVID-19 in the community were randomised using response adaptive randomisation to usual care, usual care plus doxycycline (200mg day one, then 100mg daily for six days), or usual care plus other interventions. The co-primary endpoints are time to first self-reported recovery, and hospitalisation/death related to COVID-19, both measured over 28 days from randomisation and analysed by intention to treat using Bayesian models. Trial registration: ISRCTN86534580.

Findings
The trial opened on April 2, 2020. Randomisation to doxycycline began on July 24, 2020 and was stopped on December 14, 2020, by when the trial had randomised 2689 participants overall. Of these, 2508 (93·3%) contribute data to the doxycycline primary analysis; 780 doxycycline, 948 usual care and 780 to other interventions. The mean age (standard deviation) was 61·1 (7·8) and 1409 (56·2%) were female. In the primary analysis model there was little evidence of difference in time to first self-reported recovery in the doxycycline group versus usual care (9.6 versus 10.1 days, hazard ratio 1·04 [95% Bayesian Credible Interval (BCI) 0·93 – 1·17]). The estimated benefit (95% BCI) in median time to first self-reported recovery was 0·5 [-0·99 – 2·04] days and the probability of a clinically meaningful benefit ≥1·5 days was 0·1. There were 41 (5·3%) COVID-19 related hospitalisations/deaths in doxycycline group vs 43 (4·5%) in usual care group (estimated absolute percentage difference, -0·5% [-2·6 – 1·4%]).

Interpretation
In higher-risk patients with suspected COVID-19 in the community in the UK, treatment with doxycycline was not associated with meaningful reductions in time to recovery or hospital admission, and should not be used routinely.

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Research in context (box)

Evidence before this study

A search of PubMed on February 24, 2020 using the following search terms [(randomised OR trial) AND (doxycycline OR tetracycline) AND (COVID* OR SARS-CoV-2 OR SARS-CoV)] identified 21 results, one of which reported findings from a randomised controlled trial that provided some data for the effectiveness of doxycycline as a COVID-19 treatment compared with controls/Usual Care. In this double-blind randomised controlled trial from Bangladesh, the investigators compared doxycycline (200 mg on day 1, followed by 100 mg every 12 h for the next 4 days) plus ivermectin (12 mg once daily for 5 days), ivermectin alone, and a placebo control, among 72 adults hospitalised with COVID-19 (n = 24 per arm). There was no difference in the primary outcome of time to mean duration to viral clearance in the doxycycline plus ivermectin arm (11·5 days (95% CI 9·8 – 13·2) versus the placebo arm 12·7 days (95% CI 11·3 – 14·2, p = 0·27), although time to viral clearance in the ivermectin alone arm was shorter (9·7 days (95% CI 7·8 – 11·8). A search of ClinicalTrials.gov on February 24, 2021 identified thirteen additional ongoing or completed randomised controlled trials assessing doxycycline as treatment for COVID-19 studies, none of which had reported results.

Added value of this study

To our knowledge, PRINCIPLE is the first randomised trial to report the effectiveness of doxycycline as a standalone treatment for COVID-19 patients in the community. We did not find evidence that doxycycline treatment meaningfully improved recovery or reduced hospitalisations when used in this setting.

Implications of all the available evidence

Our study, conducted among older people and those with comorbidities, does not support the routine use of doxycycline for suspected COVID-19 in the community in the absence of other indications such as bacterial pneumonia. Emerging evidence suggests bacterial co-infection in COVID-19 is uncommon, therefore antibiotic treatment is unlikely to benefit most individuals with COVID-19 in the community in developed countries and wider use without clear benefit could lead to public health harms through increased antibiotic resistance. Further research to identify strategies for diagnosing bacterial pneumonia in patients with COVID-19 in the community is needed.

Introduction

There is an urgent need to identify effective and safe treatments for coronavirus disease 2019 (COVID-19), especially for older people and those with co-morbidities who are at higher risk of hospitalisation and death.[1]

Doxycycline is a licensed, widely available, inexpensive antibiotic with a favourable safety profile that has been proposed as a COVID-19 treatment,[2,3] due to its *in vitro* activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with an EC_{50} of 4.5μM, which is consistent with lung doxycycline levels at standard oral doses of 100-200mg daily.[4] In addition, doxycycline has anti-inflammatory properties that may reduce adverse outcomes. It decreases nitrous oxide production[5] and inhibits matrix metalloproteinase 9 (MMP-9),[6] which has a role in acute respiratory distress syndrome.[7] Doxycycline may also treat bacterial super-infection, a potentially important pathway to severe COVID-19, particularly in older people or those with comorbidities.

Doxycycline has been used as a specific treatment for COVID-19 in India and Brazil,[8,9] while in the UK, national guidelines recommend doxycycline for suspected COVID-19 pneumonia in high risk patients in the community, or if bacterial aetiology is suspected.[10] The World Health Organization and the United States Centers for Disease Control and Prevention recommend antibiotics for suspected bacterial pneumonia in COVID-19, with doxycycline included in guidelines for community acquired pneumonia.[11-13] Community prescribing data from the United States and United Kingdom suggests increased use of doxycycline for respiratory tract infections during the COVID-19 pandemic,[14-17] which could exacerbate antimicrobial resistance.[18] Randomised trials evaluating doxycycline for COVID-19 are therefore needed to either demonstrate its effectiveness, or if ineffective, to prevent its unnecessary use.

We aimed to determine whether doxycycline speeds recovery or reduces hospital admission or death from COVID-19 in people at higher risk of an adverse outcome in the community.

Methods

Trial design

We assessed the effectiveness of doxycycline in the UK national, multi-centre, primary care, open-label, multi-arm, prospective adaptive Platform Randomised trial of INterventions against COVID-19 In older peoPLE (PRINCIPLE), which opened on April 2, 2020, and is ongoing. The protocol is available in the appendix (page 2). A "platform trial" allows multiple treatments for the same disease to be tested simultaneously. A master protocol defines prospective decision criteria for dropping interventions for futility, declaring interventions superior, or adding new interventions.[19] This allows the rapid assessment of multiple interventions, with the aim of rapidly dropping interventions with little evidence of meaningful benefit, and thereby directing resources towards evaluation of new interventions, with the ultimate aim of identifying community-based treatments for COVID-19. Interventions under evaluation in PRINCIPLE have included hydroxychloroquine, azithromycin, doxycycline and inhaled budesonide. Here, we report outcomes for doxycycline.

The UK Medicines and Healthcare products Regulatory Agency and the South Central-Berkshire Research Ethics Committee (Ref: 20/SC/0158), recognized by the United Kingdom Ethics Committee Authority, approved the trial protocol version 6·3, and all trial recruitment processes. Online consent is obtained from all participants. The authors vouch for the accuracy and completeness of the data and for fidelity to the protocol. An independent trial steering committee and data monitoring and safety committee provide trial oversight.

Participants

People in the community were eligible if they were aged ≥65 years, or ≥50 years with comorbidities, and had ongoing symptoms from PCR confirmed or suspected COVID-19 (in accordance with the United Kingdom National Health Service definition of high temperature and/or new, continuous cough and/or change in sense of smell/taste).[20] Symptoms must have started within the past 14 days. Co-morbidities required for eligibility in people aged 50-65 years were: weakened immune system; heart disease; hypertension; asthma or lung disease; diabetes; hepatic impairment; stroke or neurological problem; and self-reported obesity or body mass index ≥35 kg/m^2. People were ineligible to be randomised to doxycycline if they were already taking acute antibiotics or if doxycycline was contraindicated (Appendix 1 page 55). Initially, eligible people were recruited, screened and enrolled through participating general medical practices, but from May 17, 2020, people across the UK could enrol online or by telephone. After patients completed a baseline and screening questionnaire, a clinician or trained research nurse confirmed eligibility using the patients primary care medical record, accessed remotely where necessary, before conducting randomisation.

Trial interventions

The interventions reported in this manuscript are oral doxycycline 200mg on day one followed by 100mg daily for six days, or usual care. Usual care in the United Kingdom National Health Service for suspected uncomplicated COVID-19 in the community is largely supportive. Antibiotics are only recommended for suspected COVID-19 pneumonia if bacterial aetiology is suspected or the patient is at high risk, in which case guidelines recommend doxycycline.[10] In the trial, doxycycline was either prescribed or issued directly by the participant's general medical practitioner (GP), or issued centrally by the study team and delivered by urgent courier to the participant.

Trial procedures

Participants were followed up through an online, daily symptom diary for 28 days after randomisation, supplemented with telephone calls on days 2, 14 and 28. Participants were encouraged to nominate a trial partner to help provide follow up data. We obtained consent to ascertain healthcare use outcome data from general practice and hospital records. We aimed to provide a SARS-CoV-2 self-swab for PCR testing promptly after randomisation, but capacity issues early in the pandemic meant swab testing was unavailable for some participants.

Primary outcomes

The trial commenced with the primary outcome of hospitalisation or death within 28 days. However, the proportion requiring hospitalisation in the UK[21] was lower than initially expected[22]. Therefore, the trial management group and steering committee recommended amending the primary outcome to include a measure of illness duration.[23,24] Duration of illness is an important outcome for patients and has important economic and social impacts. Furthermore, treatments that do not shorten illness duration are also unlikely to demonstrate a benefit in COVID-19 related hospitalisations or deaths. This change received ethical approval on September 16, 2020, and was implemented before performing any interim analyses. Thus, the trial has two co-primary endpoints measured within 28 days of randomisation: 1) time to first reported recovery defined as the first instance that a participant reports feeling recovered; and 2) hospitalisation or death related to COVID-19.

Secondary outcomes

Secondary outcomes include a rating of how well participants feel ("How well are you feeling today? Please rate how you are feeling now using a scale of 1 – 10, where 1 is the worst you can imagine, and 10 is feeling the best you can imagine"); time to sustained recovery (date participant first reports feeling recovered and subsequently remains well until 28 days), time to initial alleviation of symptoms (date participant first reports all symptoms as minor or none), time to sustained alleviation of symptoms, time to initial reduction of severity of symptoms, contacts with health services, adherence to study treatment, the WHO-5 Well-Being Index,[25] and treatment effects among SARS-CoV-2 positive participants. We

included secondary outcomes capturing sustained recovery due to the recurrent nature of COVID-19 symptoms.

Sample size

Sample size calculations are detailed in the Adaptive Design Report (appendix page 68), where we justify sample sizes by simulating the operating characteristics of the adaptive design in multiple scenarios, which explicitly account for response adaptive randomisation, early stopping for futility/success and multiple interventions. In brief, for the primary outcome analyses, assuming a median time to recovery of nine days in the usual care group, approximately 400 participants per group would provide 90% power to detect a 2 day difference in median recovery time. Assuming 5% hospitalisation in the usual care group, approximately 1500 participants per group would provide 90% power to detect a 50% reduction in the relative risk of hospitalisation/death.

Randomisation

Eligible, consenting participants were randomised using a secure, web-based, in-house, randomisation system (Sortition). When the doxycycline group opened, the azithromycin and usual care groups were also active, with 1:1:1 allocation between the three arms, stratified by age, and comorbidity. Subsequent randomisation probabilities were determined using response adaptive randomisation via regular interim analyses, which allows allocation of more participants to interventions with better observed outcomes (Appendix 2). The trial team was blinded to randomisation probabilities.

Statistical analysis

Statistical analyses are detailed in the Master Statistical Analysis Plan (Appendix 3). The first primary outcome, time to first self-reported recovery, was analysed using a Bayesian piecewise exponential model regressed on treatment and stratification covariates, and included parameters for temporal drift. The second primary outcome, hospitalisation/death, was analysed using a Bayesian logistic regression model regressed on treatment and stratification covariates. The primary outcomes were evaluated using a "gate-keeping" strategy to preserve the overall Type I error of the primary endpoints without additional adjustments for multiple hypotheses. The hypothesis for the time-to-first-recovery endpoint is evaluated first, and if the null hypothesis is rejected, the hypothesis for the second co-primary endpoint of hospitalisation/death is evaluated. In the context of multiple interim analyses, the master protocol specifies that each null hypothesis is rejected if the Bayesian posterior probability of superiority exceeded 0·99 for the time to recovery endpoint and 0·975 (via gate-keeping) for the hospitalisation/death endpoint. Based on trials of antibiotics for lower respiratory tract infection,[26] a minimum of 1·5 days difference in median time to first report of recovery, and 2% difference in hospitalisation/mortality were pre-specified as clinically meaningful. If there is insufficient evidence of a clinically meaningful benefit in time to recovery, futility is declared and randomisation to that intervention is stopped, meaning other interventions can be evaluated more rapidly in the trial.

Bayesian methods were specified for the primary analysis for multiple reasons, including: 1) the ability to incorporate response adaptive randomisation based on a Bayesian posterior distribution of each intervention being the best intervention; 2) the ability to update Bayesian posterior distributions via interim analyses and base decisions on probabilistic summaries; and 3) the ability to account for temporal drift using Bayesian smoothing methodologies. Bayesian prior distributions were pre-specified and were chosen to allow the data to dominate model estimation.

The pre-specified primary analysis population included all eligible participants randomised to doxycycline, usual care, and other interventions, from the start of the platform trial until randomisation to doxycycline was stopped, with data extracted after a further 28 days follow-up. Because this population includes participants randomised to usual care before the doxycycline group opened, the primary analyses models include parameters to adjust for temporal drift in the study population, which may occur due to

changes in circulating SARS-CoV-2, usual care, or the pandemic situation, as well as changes in the inclusion/exclusion criteria over time. These parameters provide an estimated trajectory the primary endpoint in the Usual Care arm across time via Bayesian hierarchical modelling; methodological details are provided in the Appendix. A key sensitivity analysis includes the comparison of each intervention versus the concurrently randomized controls, which should be consistent with the primary analysis results. Although analyses for non-concurrent randomized controls are not typically implemented in traditional trials, they are becoming standard practice in many high-profile adaptive platform trials.[19,27-30] In addition, we conducted a secondary analysis restricted to SARS-CoV-2 positive participants in the primary analysis population.

Analysis of the secondary outcomes, and pre-specified sub-group analyses, were conducted on the concurrent randomisation analysis population, defined as all participants who were randomised to doxycycline or usual care, during the time period when doxycycline was open to randomisation. Secondary time-to-event outcomes were analysed using Cox proportional hazard models, and binary outcomes were analysed using logistic regression, adjusting for comorbidity status, age, duration of illness and eligibility for doxycycline at baseline.

Analyses were conducted using R (version 3·6·0) and Stata (version 16·1).

Role of the funding source
The funder had no role in the study design, data collection, analysis, interpretation nor writing of the paper, nor decision to submit for publication. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Results

Population

The first trial participant was randomised on April 2, 2020. Enrolment into the doxycycline group started on July 24, 2020. On December 14, 2020, the Trial Steering Committee, after review of planned interim analyses by the Data Monitoring and Safety Committee, advised the Trial Management Group to stop randomisation to doxycycline because the pre-specified futility criterion was met. By then, a total of 2689 people were enrolled from 1662 GP practices across the UK. 26% were enrolled directly through 223 GP practices and 74% via online/telephone contact with the study team. 827 participants were allocated to doxycycline, 1013 to usual care alone, and 849 to other treatment groups (Figure 1). The Bayesian primary analysis model includes data from all eligible participants who provided follow up data randomised to doxycycline (n = 780), usual care alone (n = 948), and other treatment groups (n = 780). To protect the integrity of the platform trial and other interventions, we only provide descriptive summaries of participants randomised to doxycycline and usual care.

The average age (range) of participants was 61 (50 – 90) years, of which 1409 (56·2%) were female and 1563 (87·5%) had co-morbidities. Median (interquartile range) duration of illness prior to randomisation was 6 (4 – 9) days. 1544 (99%) had a SARS-CoV-2 PCR result available, taken a median (interquartile range) of 4 (2 – 9) days from symptom onset, of which 791 (51·2%) were positive. Baseline characteristics were comparable between the two groups (Table 1), particularly in the concurrent analysis population (Table S1).

Follow-up information was available for 94·2% of those who received doxycycline and the concurrent controls. 84% of participants reported taking doxycycline for at least 6 days.

Primary Outcomes

Of 780 participants who received doxycycline, 596 (76·4%) reported first feeling recovered within 28 days, compared with 717 of 948 (75·6%) in usual care. Based on the Bayesian primary analysis model, that adjusts for temporal drift, the estimated median time to first recovery for doxycycline and usual care was 9.6 and 10.1 days, respectively (Table 2), (hazard ratio, 1·04; 95% Bayesian Credible Interval [BCI] [0·93 – 1·17]), equating to an estimated median benefit of 0·5 (95% BCI [-0·99 – 2·04]) days. The probability that median time to recovery was shorter in doxycycline versus usual care (i.e. probability of superiority) was 0·74 and did not meet the 0·99 threshold to declare superiority. The probability that there was a clinically meaningful benefit ≥1·5 days in time to recovery was 0·10.

A slightly higher rate of hospitalisation/deaths within 28 days follow up was observed in the doxycycline group compared to usual care (41 (5·3%) vs 43 (4·5%); estimated absolute percentage difference, -0·5%; 95% BCI, -2·6% – 1·4%) (Table 2). There were 5 deaths in the doxycycline group and 2 in usual care. The probability that hospitalisations/deaths were lower in the doxycycline versus usual care (probability of superiority) was 0·30, and was not formally analysed for significance due to gate-keeping hypothesis structure. The probability that there was a reduction in hospitalisations/deaths of at least 2% (the pre-defined threshold of a clinically meaningful benefit) was 0·005. Results of both primary outcomes were consistent in the SARS-CoV-2 infected population (time to recovery hazard ratio 1.05 [0·90 – 1·24], estimated median benefit 0.70 [-1·45 – 3·03] days, probability of meaningful benefit 0.24; hospitalisation/death estimated absolute percentage difference 1·2% [-2·7% – 5·2%], probability of meaningful benefit 0.35) (Table 2). Similarly, results of both primary outcomes were consistent in the concurrent randomisation analysis population (time to recovery hazard ratio 1·08 [0·95 – 1·23], estimated median benefit 0·57 [-0·95 – 2·13] days, probability of meaningful benefit 0.12; hospitalisation/death estimated absolute percentage difference 0.2% [-2.1%, 2.5%], probability of meaningful benefit 0.062) (Table S2).

Secondary outcomes

Analysis of secondary outcomes showed little evidence of differences between the two groups in the daily score of how well participants felt over 28 days (Table 2 and Figure S1), the WHO-5 Wellbeing Index, nor any of the hospitalisation secondary outcomes (Table 2). Similarly, there was little evidence of treatment benefit in doxycycline in time to first alleviation of symptoms, time to sustained alleviation of symptoms and time to initial reduction of severity of all symptoms and individual symptoms (Figures S2 and 3). Healthcare service use was similar between groups, and the proportions subsequently prescribed antibiotics were small (18/341 (5·3%) in the doxycycline arm, and 20/306 (6·5%) in usual care), though data for this outcome was available for less than half of participants (Table 2).

In the prespecified subgroup analyses, duration of illness prior to randomisation, baseline illness severity score, age, or comorbidity (Figure 3), did not impact the effect of doxycycline on time to first reported recovery. A treatment benefit in time to first recovery was observed in the 112 participants with no SARS-CoV-2 result available; but there was no effect in those with a positive or a negative SARS-CoV-2 test. In terms of significant adverse events, five participants reported hospitalisations unrelated to COVID-19, all in the usual care group.

Discussion

This platform, randomised trial involving participants in the community in the UK with suspected COVID-19 at higher risk of an adverse outcome, showed that doxycycline did not meaningfully shorten time to recovery or reduce hospitalisations. Findings were unchanged in secondary analysis restricted to participants with a positive test for SARS-CoV-2 infection, and in sub-group analyses by age and presence of comorbidities.

We identified no published randomised controlled trials of doxycycline as a stand-alone treatment for COVID-19. A small randomised controlled trial among 72 adults hospitalised with COVID-19 in Bangladesh compared doxycycline for five days plus single dose ivermectin, ivermectin alone for five days, and placebo .[31] The primary outcome of mean time to negative SARS-CoV-2 PCR was 12·7 days (95% CI 11·3 – 14·2) in the placebo control arm, and a similar 11·5 days (95% CI 9·8 – 13·2, p = 0·27) in the doxycycline plus ivermectin group versus placebo, and shorter in the ivermectin alone group (9·7 days, 95% CI 7·8 – 11·8, p = 0·02), and there were no differences in hospitalisation duration. A prospective observational study of 315 patients hospitalised with COVID-19 pneumonia, of whom 47% received doxycycline, found no evidence that doxycycline was associated with decreased 30 day mortality (adjusted hazard ratio 0·92, 95% CI 0·49 – 1·69, p=0·79).[32]

Strengths of our analysis include the evaluation of doxycycline as a standalone, early treatment, the focus on patients in the community at higher risk of complications, and the use of 28 days patient reported outcomes which, in the case of hospitalisation and deaths, were confirmed by medical record review. Only three-quarters of patients reported recovery during follow-up, and the median time to sustained recovery was 22 days, reflecting the now well-known potential for COVID-19 to cause recurrent and protracted symptoms, but we did not assess outcomes beyond 28 days.

A potential limitation of our study is the inclusion of patients without PCR confirmed SARS-CoV-2 infection. However, this reflects management of suspected COVID-19 early in the UK pandemic, and in many other community and low resource hospital settings, where limited SARS-CoV-2 testing may necessitate early empirical treatment. Given the variation in PCR testing sensitivity, particularly if self-administered by unwell older people in the community, some participants will have had false negative tests.[33] SARS-CoV-2 positivity within PRINCIPLE has increased as the pandemic has progressed, and our findings were unchanged when restricted to the 51·2% participants with PCR confirmed infection. We conducted an open label study as rapidly generating a placebo for multiple trial interventions was not feasible, and our study is a pragmatic trial which aims to determine whether the addition of doxycycline to usual care was effective, rather than to compare doxycycline to placebo. While this could introduce potential for bias, any possible placebo effect on time to self-reported recovery would most likely have biased results towards benefit from doxycycline. As we did not observe any meaningful benefit, this is unlikely to have influenced our results.

There was a relatively higher proportion of individuals who reported recovery on day one among those without a positive SARS-CoV-2 test. This may be an artifact of the recruitment and screening strategy that was implemented early on in the pandemic during 2020, when there were difficulties obtaining data to confirm eligibility from some general practices. This resulted in delays between trial screening and randomization for some participants, who then reported recovery sooner after randomisation. Subsequent improved screening processes enabled assessing eligibility for participation far more rapidly. The proportion differs between SARS-CoV-2 positive and negative/unknown participants due to the non-availability of testing in the early months of the trial, before screening processes were improved. These differences are taken account of in the primary analysis model which adjusts for temporal trends in time to recovery.

We found a marginally higher hazard ratio favouring doxycycline among those with confirmed SARS-CoV-2 infection and in the concurrent randomisation population, when compared to the primary analysis population which included people diagnosed on the basis of symptoms. However, the estimated benefit in terms of time to recovery was around half a day for all study populations.

In the main analysis, slightly more people were hospitalised in the doxycycline group, while in the SARS-CoV-2 positive population, there were 1.2% fewer admission/deaths in the doxycycline group, with a low probability that doxycycline was superior on this outcome. However, the hospitalisation analysis did

not account for temporal drift (in line with low event counts and the statistical analysis plan effective at time of the analysis), and the estimated difference of 1·2% may be overestimated, given increasing hospitalisation over the duration of the study. In the concurrent randomisation analysis, there was a 0.2% estimated difference in hospitalisations.

The challenge of designing trials with relatively little information early in a novel pandemic has meant that it is not unusual to update key outcomes as new information emerges.[24] Due to lower than expected hospitalisations and mortality in PRINCIPLE, and to allow measurement of effects on illness duration, the primary outcome was changed to a co-primary outcome of time to recovery, and COVID-19 related hospitalisation or death, analysed using a 'gate-keeping' approach. This change occurred before any interim analyses were performed. This approach, in which interventions that meet pre-specified futility criteria on time to recovery are stopped, assumes that interventions that lack benefit on time to recovery are unlikely to show a benefit on reducing COVID-19 hospitalisations and deaths. This enables the platform trial to cycle through multiple interventions using response adaptive randomisation, and increase the probability of achieving the trial objectives of identifying effective community treatments for COVID-19.

Doxycycline has been recommended for COVID-19,[8,9,34] particularly in people with pneumonia and those who are at higher risk of complications,[10] and there is now evidence of increased use of respiratory antibiotics including doxycycline during the COVID-19 pandemic in both the United Kingdom and United States.[14-17] Our study, conducted among older people and those with co-morbidities, with two thirds reporting shortness of breath at baseline, does not support the routine use of doxycycline for suspected COVID-19 in the community in the absence of other indications such as bacterial pneumonia. However, emerging evidence suggests bacterial co-infection in COVID-19 is uncommon,[35] therefore doxycycline is unlikely to benefit most individuals with COVID-19 in developed countries. Wider use could lead to public health harms through increased antibiotic resistance.[18] Further research into strategies to identify bacterial co-infection in the community are needed to allow targeted, appropriate use of antibiotics in COVID-19.

In conclusion, in higher-risk patients with suspected COVID-19 in the community in the UK, treatment with doxycycline was not associated with meaningful reductions in time to recovery or hospital admission/death.

Trial management group contributions

CCB and FRDH had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. CCB and FDRH decided to publish the paper. BS, NB, L-MY, CCB, FDRH, SG, RD, JK, GH, OVH, OG, JD, GD, MJL contributed to trial design. SdeL, MA, MJL, PHE, NT and SH helped plan the trial. EO, HS, EB, JA, ST, NT, PHE, HR, SdeL, MP, JG, were responsible for acquisition of data. CCB, FDRH, LMY, BS, JD, GH, OVH and OG drafted the manuscript. BS, NB, L-MY, MD, MF, CS, and VH contributed to statistical analysis. DJ designed the information systems. JG led data management. All members of the PRINCIPLE writing group critically revised the manuscript. The members of the PRINCIPLE Trial Collaborative Group and their roles in the conduct of the trial are listed below.

Conflict of Interest statement

BS, MD, CS, MF and NB report grants from The University of Oxford, for the Sponsor's grant from the UK NIHR, for statistical design and analyses for the PRINCIPLE trial during the conduct of the study. RD reports grants and personal fees from Synairgen during the conduct of the study, personal fees from TEVA Pharmaceuticals, Sanofi, Boehringer, and Novartis outside the submitted and grants from the Innovative Medicines Initiative, the UK Medical Research Council and Novartis outside the submitted

work. FDRH reports grants from UKRI during the conduct of the study. OVH reports grants from UKRI outside the submitted work. All other authors have no competing interests to declare.

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Data Sharing
Data can be shared with qualifying researchers who submit a proposal with a valuable research question as assessed by a committee formed from the TMG including senior statistical and clinical representation. A contract should be signed.

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Table 1 Baseline characteristics of all eligible, randomised participants by treatment group

	Doxycycline (N=798)	Usual Care (N=994)	Total (N=1792)
Age (year), mean(SD)	61·3 (7·7)	60·9 (7·9)	61·1 (7·9)
Greater than or equal to 65 years	303 (38·0%)	359 (36·1%)	
Less than 65 years	495 (62·0%)	635 (63·9%)	
Sex, n(%)			
Female	439 (55·0%)	560 (56·3%)	999 (55·7%)
Male	358 (44·9%)	432 (43·5%)	790 (44·1%)
Missing, n(%)	1 (0·1%)	2 (0·2%)	3 (0·2%)
Ethnicity*, n(%)			
White	739 (92·6%)	820 (82·5%)	1559 (87·0%)
Mixed background	8 (1·0%)	22 (2·2%)	30 (1·7%)
South Asian	43 (5·4%)	45 (4·5%)	88 (4·9%)
Black	6 (0·8%)	5 (0·5%)	11 (0·6%)
Other	2 (0·3%)	10 (1·0%)	12 (0·7%)
Missing, n(%)	0 (0·0%)	92 (9·3%)	92 (5·1%)
Index of multiple deprivation quintile			
(Most deprived) 1	183 (22·9%)	241 (24·3%)	424 (23·7%)
2	152 (19·1%)	190 (19·1%)	342 (19·1%)
3	159 (19·9%)	189 (19·0%)	348 (19·4%)
4	154 (19·3%)	196 (19·7%)	350 (19·5%)
(Least deprived) 5	149 (18·7%)	176 (17·7%)	325 (18·1%)
Missing	1 (0·1%)	2 (0·2%)	3 (0·2%)
Duration of illness prior to randomisation (days), median (interquartile range)	6 (4 - 9)	6 (4 – 9)	6·0 (4·0 – 9·0)
Smoking status, n(%)			
Current smoker	74 (9·3%)	125 (12·6%)	199 (11·1%)
Former smoker	309 (38·7%)	367 (36·9%)	676 (37·7%)
Never smoker	404 (50·6%)	476 (47·9%)	880 (49·1%)
Missing, n(%)	11 (1·4%)	26 (2·6%)	37 (2·1%)
Swab result, n(%)			
Negative	293 (36·7%)	460 (46·3%)	753 (42·0%)
Positive	442 (55·4%)	349 (35·1%)	791 (44·1%)
No result	9 (1·1%)	7 (0·7%)	16 (0·9%)
Not available, n(%)	54 (6·8%)	178 (17·9%)	232 (12·9%)
Comorbidity, n(%)	697 (87·3%)	866 (87·1%)	1563 (87·2%)
Comorbidities			
Asthma, COPD or lung disease, n(%)	304 (38·1%)	364 (36·6%)	668 (37·3%)
Diabetes, n(%)	134 (16·8%)	188 (18·9%)	322 (18·0%)
Heart problems†, n(%)	107 (13·4%)	148 (14·9%)	255 (14·2%)
High blood pressure required medication, n(%)	318 (39·8%)	425 (42·8%)	743 (41·5%)
Liver disease, n(%)	18 (2·3%)	24 (2·4%)	42 (2·3%)
Stroke or other neurological problem, n(%)	53 (6·6%)	58 (5·8%)	111 (6·2%)
Taking ACE inhibitor‡, n(%)	163 (20·4%)	204 (20·5%)	367 (20·5%)
Baseline symptoms			
Fever, n(%)			
No problem	377 (47·2%)	432 (43·5%)	809 (45·1%)
Minor problem	247 (31·0%)	339 (34·1%)	586 (32·7%)
Moderate problem	156 (19·5%)	198 (19·9%)	354 (19·8%)
Major problem	18 (2·3%)	25 (2·5%)	43 (2·4%)
Cough, n(%)			
No problem	162 (20·3%)	170 (17·1%)	332 (18·5%)
Minor problem	320 (40·1%)	393 (39·5%)	713 (39·8%)
Moderate problem	275 (34·5%)	371 (37·3%)	646 (36·0%)
Major problem	41 (5·1%)	60 (6·0%)	101 (5·6%)
Shortness of breath, n(%)			
No problem	339 (42·5%)	327 (32·9%)	666 (37·2%)
Minor problem	303 (38·0%)	431 (43·4%)	734 (41·0%)
Moderate problem	134 (16·8%)	213 (21·4%)	347 (19·4%)
Major problem	22 (2·8%)	23 (2·3%)	45 (2·5%)
Muscle ache, n(%)			
No problem	246 (30·8%)	298 (30·0%)	544 (30·4%)
Minor problem	294 (36·8%)	376 (37·8%)	670 (37·4%)
Moderate problem	203 (25·4%)	238 (23·9%)	441 (24·6%)
Major problem	55 (6·9%)	82 (8·2%)	137 (7·6%)
Nausea, n(%)			
No problem	604 (75·7%)	743 (74·7%)	1347 (75·2%)

	Doxycycline (N=798)	Usual Care (N=994)	Total (N=1792)
Minor problem	138 (17·3%)	205 (20·6%)	343 (19·1%)
Moderate problem	45 (5·6%)	38 (3·8%)	83 (4·6%)
Major problem	11 (1·4%)	8 (0·8%)	19 (1·1%)
Feeling generally unwell (malaise), n(%)			
No problem	60 (7·5%)	52 (5·2%)	112 (6·3%)
Minor problem	357 (44·7%)	333 (33·5%)	690 (38·5%)
Moderate problem	322 (40·4%)	321 (32·3%)	643 (35·9%)
Major problem	59 (7·4%)	61 (6·1%)	120 (6·7%)
Diarrhoea, n(%)			
No problem	598 (74·9%)	577 (58·0%)	1175 (65·6%)
Minor problem	150 (18·8%)	134 (13·5%)	284 (15·8%)
Moderate problem	39 (4·9%)	44 (4·4%)	83 (4·6%)
Major problem	11 (1·4%)	12 (1·2%)	23 (1·3%)
Taken antibiotics since illness started, n(%)	14 (1·8%)	41 (4·1%)	55 (3·1%)
Use of any healthcare services			
GP, n(%)	185 (23·2%)	279 (28·1%)	464 (25·9%)
Other primary care services, n(%)	35 (4·4%)	66 (6·6%)	101 (5·6%)
NHS 111, n(%)	106 (13·3%)	179 (18·0%)	285 (15·9%)
A&E, n(%)	8 (1·0%)	14 (1·4%)	22 (1·2%)
Other healthcare services, n(%)	13 (1·6%)	30 (3·0%)	43 (2·4%)
Well-being (WHO5 Questionnaire)§, mean(SD)	53·3 (24·6)	49·5 (24·5)	51·2 (24·6)
Missing, n(%)	0 (0·0%)	24 (1·3%)	24 (1·3%)

* Data on ethnicity were collected retrospectively via notes review before July 2020

† E.g. angina, heart attack, heart failure, atrial fibrillation, valve problems

‡ Such as Ramipril, Lisinopril, Perindopril, Captopril or Enalapril

§ Well-being is measured using the WHO well-being index which includes 5 items relating to well-being measured on a five point scale. A total score is computed by summing the scores to the five individual questions to give a raw score ranging from 0 to 25 which is then multiplied by 4 to give the final score from 0 representing the worst imaginable well-being to 100 representing the best imaginable well-being.

Table 2: Primary and Secondary Outcomes

	Doxycycline	Usual Care	Estimated benefit Median TTR/Hosp rate (95% BCI)	Hazard Ratio/ Odds Ratio (95% BCI)	Pr(Meaningful effect)	Pr(Superiority)
Model-based Estimates, Primary outcomes (Primary analysis population)						
Time to first reported recovery (days)	9.6 (8.3, 11.0)*	10.1 (8.7, 11.7)*	0·50 (-0·99 – 2·04)*	1.04 (0.93,1.17)*	0·10*	0·74*
Hospitalisation/death at 28 days, n (%)	5.1% (3.6%, 6.8%)†	4.6% (3.4%, 6.1%)	-0·5% (-2·6% – 1·4%)†	1.13 (0.73, 1.74)†	0·005†	0·30†
Model-based Estimates, Primary outcomes (SARS-CoV-2 positive analysis population)						
Time to first reported recovery, median (IQR)	11.8 (10.3, 13.7)*	12.5 (10.8, 14.8)*	0·70 (-1·45 – 3·03)*	1.05 (0.90,1.24)*	0·24*	0·74*
Hospitalisation/death at 28 days, n (%)	8.0% (5.7%, 10.8%)†	9.2% (6.6%, 12.6%)†	1·2% (-2·7% – 5·2%)†	0.85 (0.52, 1.42)†	0·35†	0·73†
Secondary outcomes‡	**Doxycycline**	**Usual Care**	**Estimated treatment effect (95% CI)**		**P-value**	
Sustained recovery, n/N (%)	502/780 (64·4%)	396/644 (61·5%)				
Time to sustained recovery, median (IQR)	22 (9, -)	22 (8, -)	1·00 (0·88 – 1·14)§		0·96	
Alleviation of all symptom, n/N (%)	618/671 (92%)	522/551 (94·7%)				
Time to alleviation of all symptom, median (IQR)	3 (2, 7)	3 (1, 8)	0·96 (0·86 – 1·09)§		0·55	
Sustained alleviation of all symptom, n/N (%)	542/648 (83·6%)	428/515 (83·1%)				
Time to sustained alleviation of all symptom, median (IQR)	8 (3 – 23)	10(3 – 23)	1·03 (0·90 – 1·17)§		0·68	
Initial reduction of severity of symptom, n/N (%)	701/780 (89·9%)	572/644 (88·8%)				
Time to initial reduction of severity of symptom, median (IQR)	5 (1 – 12)	4 (1 – 11)	0·99 (0·88 – 1·11)§		0·84	
Rating of how well participant feels (1 worst, 10 best), mean (SD) [n]						
Day 7	7·1 (1·9) [757]	7·0 (1·9) [636]	0·05 (-0·16 – 0·25)ll		0·66	
Day 14	7·8 (1·7) [752]	7·7 (1·7) [632]	0·06 (-0·16 – 0·28)ll		0·58	
Day 21	8·1 (1·6) [689]	8·0 (1·6) [566]	0·00 (-0·25 – 0·25)ll		0·99	
Day 28	8·3 (1·5) [754]	8·3 (1·5) [629]	-0·06 (-0·34 – 0·22)ll		0·69	
Well-being (WHO5 Questionnaire), mean (SD)[n]						
Day 14	45·4 (24·1) [738]	44·3 (23·9) [616]	0·20 (-2·06 – 2·45)ll		0·86	
Day 28	54·5 (23·2) [737]	53·8 (23·7) [605]	0·01 (-2·25 – 2·28)ll		0·99	
Self-reported contact with ≥1 healthcare service	381/773 (49·3%)	314/642 (48·9%)	1·04 (0·84 – 1·29)¶		0·72	
GP reported contact with ≥1 healthcare service	203/381 (53·3%)	181/345 (52·5%)	0·99 (0·73 – 1·34)¶		0·96	
Prescription of antibiotics	18/341 (5·3%)	20/306 (6·5%)	0·81 (0·44 – 1·50)**		0·51	
Hospital assessment without admission	8/767 (1·0%)	11/628 (1·8%)	0·60 (0·24 – 1·47)**		0·35	
Oxygen Administration	24/757 (3·2%)	20/621 (3·2%)	0·98 (0·55 – 1·76)**		>0·99	
Mechanical ventilation	3/757 (0·4%)	5/621 (0·8%)	0·49 (0·12 – 2·05)**		0·48	
ICU admission	4/755 (0·5%)	6/620 (1·0%)	0·55 (0·16 – 1·93)**		0·36	

* Model-based estimates median time to first reported recovery (95% Bayesian credible interval). Estimated benefit in median time to recovery derived from a Bayesian piecewise exponential model adjusted for age and comorbidity at baseline, with 95% Bayesian credible interval. A positive value in estimated benefit in median time to recovery (or HR > 1) corresponds to a reduction in time to recovery in days in doxycycline compared to Usual Care. Pr(Meaningful effect) is the model-based estimated probability that the benefit in median time to recovery compared to Usual Care is at least 1·5 days. Pr(Superiority) is the probability of superiority and treatment superiority is declared if Pr(superiority) ≥ 0.99 versus usual care.

† Model-based estimates percentage of hospitalisation/death at 28 days (95% Bayesian credible interval). Estimated benefit, expressed as difference percentage, in hospitalisation/death is derived from a Bayesian logistic regression model adjusted for age and comorbidity at baseline, with 95% Bayesian credible interval. A positive value in the estimated difference percentage (or OR < 1) favours doxycycline. Pr(Meaningful effect) is the model-based estimated probability that the benefit in hospitalisation/death compared to Usual Care is at least 2%. Pr(Superiority) is the probability of superiority and treatment superiority is declared if Pr(superiority) ≥ 0·975 versus usual care

‡ All secondary outcome analyses were conducted on the concurrent randomisation analysis population, but restricted to those in the doxycycline and usual care group only.

§ Estimated hazard ratio derived from a Cox proportional hazard model adjusted for age, comorbidity at baseline, duration of illness, and eligible for doxycycline at baseline, with 95% confidence interval.

ll Mixed effect model adjusting age, comorbidity, duration of illness, eligible for doxycycline at baseline, and time. Participant was fitted as a random effect. WHO well-being score was also adjusted for the score at baseline

¶ Relative risk adjusted for age, comorbidity at baseline, duration of illness, and eligible for doxycycline at baseline

** Unadjusted relative risk due to low event rate.

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