National Institute for Health and Care Excellence

NICE COVID-19 rapid guideline: managing COVID-19

[C] Evidence review for doxycycline

NICE guideline NG191

September 2021

Guideline version (Final)

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Objective

This evidence review aims to evaluate the clinical effectiveness of doxycycline in people with COVID-19.

Review question

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see appendix A for more information). The review question for this evidence review is:

What is the effectiveness and safety of doxycycline for acute symptoms and complications of COVID-19?

Methodology

The evidence review was developed using NICE interim process and methods for guidelines developed in response to health and social care emergencies.

Included studies

NICE's information services team identified relevant evidence through focused evidence searches up to 27 May 2021 (see appendix B for full details). The search identified 55 references. These references were screened using their titles and abstracts and 1 full text reference was obtained and assessed for relevance against the criteria in the PICO. This study was included in the evidence review.

Results

Key results

The evidence suggests that doxycycline plus standard care does not give statistically significant improvements in hospitalisation/death, mechanical ventilation, oxygen administration, ICU admission, measures of symptom alleviation and recovery, or significant adverse events in people with COVID-19 in the community.

What is the evidence informing this conclusion?

These findings are based on 1 RCT (PRINCIPLE) (Butler 2021). This UK study recruited participants from the community with ongoing symptoms (starting within the last 14 days) from PCR-confirmed or suspected COVID-19. Participants were aged 65 years and above or aged 50 years and above with comorbidities.

The RCT compared doxycycline plus standard care (N=780) with standard care (N=948) in adults with COVID-19. In December 2020 randomisation to doxycycline was stopped as pre-specified futility criteria were met.

Publication status

All studies have been peer-reviewed.

Study characteristics

Participants were recruited from the community (from general practices, online, or by telephone). Eligible participants had ongoing symptoms from PCR-confirmed or suspected COVID-19 (that must have started within the last 14 days) (in accordance with the United Kingdom [UK] National Health Service [NHS] definition of high temperature and/or new, continuous cough and/or change in sense of smell/taste). Eligible participants were aged 65 years and older, or 50 years and older if they had comorbidities (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/m2.) People who were already taking acute antibiotics were excluded.

The intervention was doxycycline 200mg on day one, followed by 100mg daily for six days. Standard care for suspected uncomplicated COVID-19 in the community in the

UK NHS is largely supportive (antibiotics only being recommended for suspected COVID-19 pneumonia if bacterial aetiology is suspected or the patient is at high risk, in which instance guidelines recommend doxycycline).

The proportion of people with a positive swab result varied from 35.1% (standard care group) to 55.4% (doxycycline group). Participants had a mean (standard deviation [SD]) age of 61.1 (7.9) years; over half (55.7%) were female and the majority (87.2%) had comorbidities. The median (interquartile range [IQR]) duration of illness prior to randomisation was 6 (4–9) days.

What are the main results?

Hospitalisation/death within 28 days (critical outcome)

One RCT (Butler 2021) found no statistically significant difference in hospitalisation/death within 28 days with doxycycline plus standard care compared with standard care (7 more per 1000 patients; OR 1.13 [95% CI 0.73 — 1.74]) in people with COVID-19 in the community.

Mechanical ventilation (critical outcome)

One RCT (Butler 2021) reported no statistically significant difference in mechanical ventilation within 28 days with doxycycline plus standard care compared with standard care (4 fewer per 1000 patients; RR 0.49 [95% CI 0.12 — 2.05]) in people with COVID-19 in the community.

Significant adverse events (critical outcome)

One RCT (Butler 2021) showed no statistically significant difference in significant adverse events with doxycycline plus standard care compared with standard care (5 fewer per 1000; RR 0.11 [95% CI 0.01 — 1.99]) in people with COVID-19 in the community.

Oxygen administration (important outcome)

One RCT (Butler 2021) reported no statistically significant difference in oxygen administration within 28 days with doxycycline plus standard care compared with

standard care (1 fewer per 1000 patients; RR 0.98 [95% CI 0.55 — 1.76]) in people with COVID-19 in the community.

ICU admission (important outcome)

One RCT (Butler 2021) found no statistically significant difference in ICU admission within 28 days with doxycycline plus standard care compared with standard care (5 fewer per 1000; RR 0.55 [95% CI 0.16 — 1.93]) in people with COVID-19 in the community.

Alleviation of all symptoms within 28 days (important outcome)

One RCT (Butler 2021) found a non statistically significant improvement in alleviation of symptoms within 28 days with doxycycline plus standard care compared with standard care (28 fewer per 1000; RR 0.97 [95% CI 0.94 — 1.00]) in people with COVID-19 in the community.

Initial reduction of severity of symptoms within 28 days (important outcome)

One RCT (Butler 2021) found no statistically significant difference of initial reduction of severity of symptoms within 28 days with doxycycline plus standard care compared with standard care (11 more per 1000; RR 1.01 [95% CI 0.98 — 1.05]) in people with COVID-19 in the community.

Sustained alleviation of all symptoms within 28 days (important outcome)

One RCT (Butler 2021) found no statistically significant difference in alleviation of all symptoms within 28 days with doxycycline plus standard care compared with standard care (5 more per 1000; RR 1.01 [95% CI 0.96 — 1.06]) in people with COVID-19 in the community.

Sustained recovery (important outcome)

One RCT (Butler 2021) found no statistically significant difference in sustained recovery within 28 days with doxycycline plus standard care compared with standard care (29 more per 1000; RR 1.05 [95% CI 0.97— 1.13]) in people with COVID-19 in the community.

Time to initial reduction of severity of symptoms (important outcome)

One RCT (Butler 2021) reported no statistically significant difference in time to initial reduction of severity of symptoms with doxycycline plus standard care (HR 0.99 [95% CI 0.88 — 1.11]) compared with standard care in people with COVID-19 in the community.

Time to alleviation of all symptoms (important outcome)

There was no statistically significant difference in time to alleviation of all symptoms with doxycycline plus standard care compared with standard care (HR 0.96 [95% CI 0.86 — 1.09]) in 1 RCT (Butler 2021) in people with COVID-19 in the community.

Time to sustained alleviation of all symptoms (important outcome)

There was no statistically significant difference in 1 RCT (Butler 2021) for time to initial reduction of severity of symptoms with doxycycline plus standard care compared with standard care (HR 1.03 95% CI 0.90 — 1.17]) in people with COVID-19 in the community.

Time to first reported recovery (important outcome)

One RCT (Butler 2021) showed no statistically significant difference in time to first reported recovery with doxycycline plus standard care compared with standard care (HR 1.04 [95% CI 0.93 — 1.17]) in people with COVID-19 in the community.

Time to sustained recovery (important outcome)

One RCT (Butler 2021) found no statistically significant difference in time to sustained recovery with doxycycline plus standard care compared with standard care (HR 1.00 95 CI 0.88 — 1.14]) in people with COVID-19 in the community.

See appendix G for full GRADE profiles and see appendix F for forest plots.

Our confidence in the results

The certainty of evidence for the critical outcomes of hospitalisation/death, mechanical ventilation and significant adverse events was rated as moderate (due to serious imprecision).

The certainty of evidence for the important outcome of alleviation of all symptoms at 28 days was considered to be high. However, the certainty of evidence for all remaining important outcomes was rated as moderate due to serious imprecision.

Evidence to decision

Benefits and harms

The panel discussed evidence from a trial comparing doxycycline plus standard care with standard care alone to treat COVID-19 in the community in people 65 years and over or people 50 and over if they have comorbidities. They agreed that the evidence suggests that, in these groups, doxycycline plus standard care does not reduce the risk of hospitalisation and death, admission into intensive care, the need for mechanical ventilation or oxygen, or significant adverse events. They also agreed that the evidence suggests doxycycline does not improve symptoms or recovery. The panel noted the lack of statistically significant benefits with doxycycline in both the main analysis population and the analysis in people with laboratory-confirmed positive COVID-19. The panel were aware that randomisation to doxycycline in the trial was stopped because of futility in December 2020. No evidence was identified for other groups or settings.

The panel noted that doxycycline may cause side effects such as gastrointestinal disturbances and photosensitivity. They were also concerned that using doxycycline to treat COVID-19 in the community may increase risk of antimicrobial resistance, which could have important antibiotic stewardship implications.

Certainty of the evidence

The certainty of evidence was rated as moderate because of serious imprecision (apart from 1 outcome that was rated as high). The panel were aware of imprecision issues, including there being only 1 study, the confidence intervals crossing the line of no effect and few events for some outcomes.

The panel were unclear on which symptoms were included in the measures of symptom alleviation and recovery.

The panel also discussed the relatively low proportion of people in the trial with laboratory-confirmed COVID-19. They thought this reflected the pragmatic treatment of COVID-19 in the community in the early stages of the pandemic, which was based on the presence of symptoms and limited testing capacity. However, they noted that testing is now more widely available in the community.

Because there are potential harms from doxycycline use (side effects and risk of antimicrobial resistance), the panel made a strong recommendation against use in the community.

Values and preferences

The panel were not aware of any systematically collected data on preferences and values. They noted the importance to people with COVID-19 in the community of avoiding hospital admission. However, the included trial only reported a composite outcome of hospitalisation and death, and reported hospital assessment without admission but not hospitalisation. Avoiding admission into intensive care was also considered an important outcome by the panel. They inferred that most people would not choose doxycycline because of the lack of meaningful benefit in treating COVID-19, the potential for side effects and the risk of antimicrobial resistance.

Resources

Cost effectiveness was not assessed as part of the evidence review.

Equity

No evidence was found in people under 65 years, people under 50 years with comorbidities or pregnant women. However, because the overall recommendation is not to offer doxycycline to anyone in the community, it is not expected to cause inequity among any groups.

Acceptability

The panel were not aware of any systematically collected evidence about acceptability. However, the evidence does not suggest benefits with doxycycline and there are potential harms (from side effects and a risk of promoting antimicrobial resistance). So, its use in the community is not likely to be acceptable unless there are other licensed indications for which its use remains appropriate.

Feasibility

The panel were not aware of any systematically collected evidence about feasibility.

Appendices

Appendix A: PICO table

PICO table

What is the effectiveness and safety of pharmacological and non-pharmacological treatments for acute symptoms and complications of COVID-19?

Criteria	Notes
Population	Adults, young people and children with suspected or confirmed COVID-19.
Interventions	Pharmacological and non-pharmacological treatments that has the potential to be used to treat COVID-19
Comparators	• Standard care alone, standard care plus placebo, placebo or active comparator Note: Standard care comprises best supportive care and in certain circumstances the use of additional drugs (such as dexamethasone, remdesivir).
Outcomes	Those marked with an * are critical outcomes • All-cause mortality (n/N)* • Duration of invasive mechanical ventilation (IMV) (days)* • IMV or death (composite) (n/N)* • IMV (number of patients requiring IMV who were not already receiving IMV at randomisation) (n/N)* • Number of patients experiencing one or more serious adverse events (n/N)* • Reduction in hospitalisation* • Duration of supplemental oxygen (days) • NIC/HFNO (number of patients requiring NIV/HFNO who were not already receiving NIV/HFNO at randomisation) (n/N) • Supplemental oxygen (number of patients requiring supplemental oxygen who were not already receiving supplemental oxygen at randomisation) (n/N) • Number of patients experiencing one or more adverse events (n/N)

	• Number of patients who discontinued treatment due to an adverse event (n/N) • Number of patients experiencing septic shock (n/N) • Number of patients experiencing resolution of dyspnoea/breathlessness (n/N) • Number of patients requiring hospitalization (n/N) • Number of patients requiring admission to intensive care (n/N) • Duration of hospital stay (days) • Number of patients discharged from hospital (n/N) • Virological clearance (number of patients returning a negative PCR) (n/N) • Number of patients who experienced clinical recovery (resolution of symptoms or number of patients within category 1 of an ordinal scale [non-hospitalised and returned to normal life]) • Time to recovery (days) • Number of patients who experienced clinical improvement (measured by a one or two point decrease on a 6-8 point ordinal scale, or defined as a reduction in disease severity [e.g. 'severe' to 'mild' illness]) (n/N) • Time to improvement (days) • Number of patients who experienced clinical deterioration (measured by a one or two point increase on a 6-8 point ordinal scale, or defined as an increase in disease severity [e.g. 'mild' to 'severe' illness]) (n/N) • Time to deterioration (days) • Longer-term outcomes reported in the study such as functional independence The definitions of mechanical ventilation, non-invasive ventilation and other forms of respiratory support such as high flow nasal oxygen (HFNO) therapy or continuous positive airway pressure or non-invasive bilevel ventilation may differ across the studies. In the context of UK practice the following definitions should be considered: **Advanced respiratory support:** Invasive mechanical ventilation, bilevel positive airway pressure (BiPAP) via translaryngeal tube or

	tracheostomy, continuous positive airway pressure (CPAP) via translaryngeal tube, or extracorporeal respiratory support) **Non-invasive ventilation:** includes HFNO, CPAP, CPAP via tracheostomy, and non-invasive bilevel ventilation. Note: oxygen via (low flow) nasal cannulae or face mask does not fall within the categories above.
Settings	All settings
Subgroups	• Adults > 50 years • Children <12 years of age • Disease severity (moderate/severe/critical) • Gender • Ethnic background • Pregnant women • Comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity) • Time from symptom onset • Treatment with other therapeutics used for COVID-19
Study types	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs If no systematic reviews or RCT evidence is available progress to: • non-randomised controlled trials • systematic reviews of non-randomised controlled trials • cohort studies • before and after studies • interrupted time series studies Preprints will be considered as part of the evidence review.
Countries	Any
Timepoints	From 2020 onwards

Other exclusions	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: • non-English language papers, studies that are only available as abstracts, and narrative reviews • animal studies • editorials, letters, news items, case reports and commentaries, conference abstracts and posters • theses and dissertations
Equality issues	Sex, age, ethnicity, religion or beliefs, people with a learning disability and disabled people, socioeconomic status, people who are pregnant or breastfeeding, people whose first language isn't English, people who are homeless, refugees, asylum seekers, migrant workers and people who are homeless.

Appendix B: Literature search strategy/Data source

Database	Platform	Segment searched	Saved search name
MEDLINE ALL	Ovid	1946 to May 26, 2021	NG191_Doxycycline_Medline All
Embase	Ovid	1974 to 2021 May 26	NG191_Doxycycline_Embase
Cochrane Library	Wiley	Issue 4 of 12, April 2021	NG191_Doxycycline_CENTRAL
Pre-prints – bioRxiv and medRxiv	RIS via EPPI	IS surveillance - pre-prints v3	N/A

Source	No. of results	Total results	Total after deduplication
MEDLINE ALL	7	64	55
Embase	21		
Cochrane - CENTRAL	24		
Preprints	12		

Database search strategies

Medline All Strategy

1 Doxycycline/ (10046)
2 (doxycyclin* or "Vibramycin-D" or "Efracea" or "Adjusan" or "Doxyhexal" or "Periostat").ti,ab. (14483)
3 1 or 2 (17971)
4 (NCT04434144 or NCT04482686 or NCT04370782).af. (0)
5 (NCT04371952 or NCT04407130 or NCT04433078).af. (0)
6 ("IRCT20200418047121N1" or NCT04403555 or NCT04349410).af. (0)
7 (NCT04715295 or "2020-001209-22").af. (0)
8 or/4-7 (0)
9 3 or 8 (17971)
10 randomized controlled trial.pt. (531897)
11 randomi?ed.mp. (939155)
12 placebo.mp. (225410)
13 or/10-12 (1000098)
14 SARS-CoV-2/ or COVID-19/ (81467)
15 (corona* adj1 (virus* or viral*)).ti,ab,kw,kf. (3458)
16 (CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff

volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab,kw,kf. (48166)
17 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab,kw,kf. (149805)
18 or/14-17 (153738)
19 limit 18 to yr="2020-Current" (140424)
20 (19 and english.lg.) not (letter or historical article or comment or editorial or news or case reports).pt. not (Animals/ not humans/) (99960)
21 9 and 13 and 20 (7)

Embase Strategy

1 doxycycline hyclate/ or doxycycline/ or doxycycline fosfatex/ (56651)
2 (doxycyclin* or "Vibramycin-D" or "Efracea" or "Adjusan" or "Doxyhexal" or "Periostat").ti,ab. (21404)
3 1 or 2 (58959)
4 (NCT04434144 or NCT04482686 or NCT04370782).af. (8)
5 (NCT04371952 or NCT04407130 or NCT04433078).af. (8)
6 ("IRCT20200418047121N1" or NCT04403555 or NCT04349410).af. (12)
7 (NCT04715295 or "2020-001209-22").af. (0)
8 or/4-7 (24)
9 3 or 8 (58976)
10 random:.tw. (1665380)
11 placebo:.mp. (474478)
12 double-blind:.tw. (220054)
13 or/10-12 (1926418)
14 exp severe acute respiratory syndrome coronavirus 2/ or coronavirus disease 2019/ or experimental coronavirus disease 2019/ (117521)
15 (corona* adj1 (virus* or viral*)).ti,ab,kw. (2746)
16 (CoV not (Coefficien* or co-efficien* or covalent* or covington or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk" or CoVR or CoVS)).ti,ab,kw. (46638)
17 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab,kw. (147090)
18 or/14-17 (157409)
19 limit 18 to yr="2020-Current" (142228)
20 (19 and english.lg.) not (letter or editorial or conference).pt. not (nonhuman/ not human/) not "case report".sh. not medline*.db. (63108)
21 9 and 13 and 20 (21)

Cochrane CENTRAL strategy

#1 MeSH descriptor: [Doxycycline] explode all trees 1078
#2 (doxycyclin* or "Vibramycin-D" or "Efracea" or "Adjusan" or "Doxyhexal" or "Periostat"):ti,ab 1981
#3 #1 or #2 2097
#4 (NCT04434144 or NCT04482686 or NCT04370782):ti,ab,kw 0

#5 (NCT04371952 or NCT04407130 or NCT04433078):ti,ab,kw 0
#6 ("IRCT20200418047121N1" or NCT04403555 or NCT04349410):ti,ab,kw 0
#7 (NCT04715295 or "2020-001209-22"):ti,ab,kw 0
#8 {or #4-#7} 0
#9 #3 or #8 2097
#10 MeSH descriptor: [SARS-CoV-2] this term only 251
#11 MeSH descriptor: [COVID-19] this term only 337
#12 (corona* near/1 (virus* or viral*)):ti,ab,kw 219
#13 (CoV NOT (Coefficien* or "co-efficient" or “co-efficiency” or “co-efficiencies” or covalent* or Covington* or covariant* or covarianc* or "cut-off value" or "cut-off values" or "cutoff value" or "cutoff values" or "cut-off volume" or "cut-off volumes" or "cutoff volume" or "cutoff volumes" or "combined optimisation value" or "combined optimisation values" or "combined optimization value" or "combined optimization values" or "central vessel trunk" or "central vessel trunks" or CoVR or CoVS)):ti,ab,kw 397
#14 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or covid19 or covid-19 or covid):ti,ab,kw 5363
#15 {or #10-#14} with Cochrane Library publication date Between Jan 2020 and Dec 2021, in Cochrane Reviews 32
#16 {or #10-#14} with Publication Year from 2020 to 2021, in Trials 5158
#17 #15 OR #16 5190
#18 #9 and #17 24

Pre-print server	
Name	medRxiv and bioRxiv
URL	EPPI Review Version 3
Date completed	28th May 2021, 8:14am
Search terms used in EPPI	The following terms were searched on Title and abstract (combined with OR): • Doxycycline Efracea Adjusan Doxyhexal Periostat • "Vibramycin-D" "Vibramycin D" [phrase] • NCT04434144 NCT04482686 NCT04370782 • NCT04371952 NCT04407130 NCT04433078 • IRCT20200418047121N1 NCT04403555 NCT04349410 • NCT04715295 • "2020-001209-22" "2020 001209 22" [phrase]
Results	12

Search notes

The searches were created using the COVID TS searches for Doxycycline. Additional trial numbers were included (line 7). As agreed the searches were limited to RCTs only.

Appendix C: Included studies

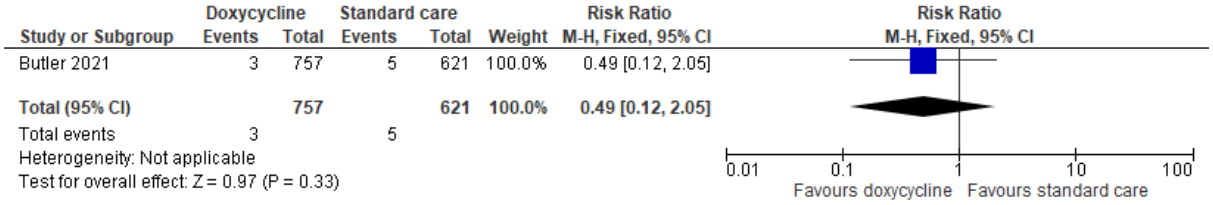
Butler CC, Yu L-M, Dorward J et al : Doxycycline for community treatment of suspected COVID-19 in people at high risk of adverse outcomes in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. The Lancet. Respiratory medicine 2021 9 (9):1010-1020,

Appendix D: Forest Plots

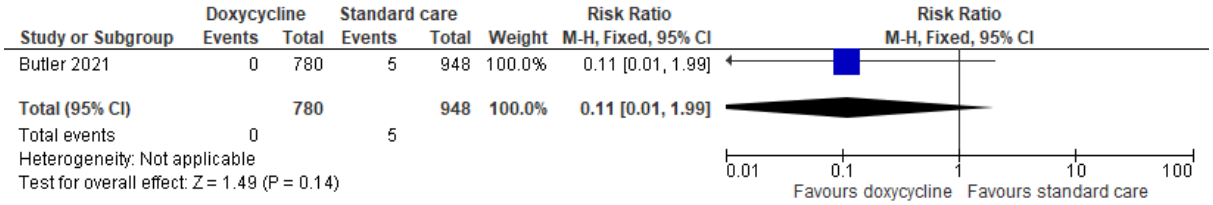
Hospitalisation/ death within 28 days

No forest plot. Data as reported in study.

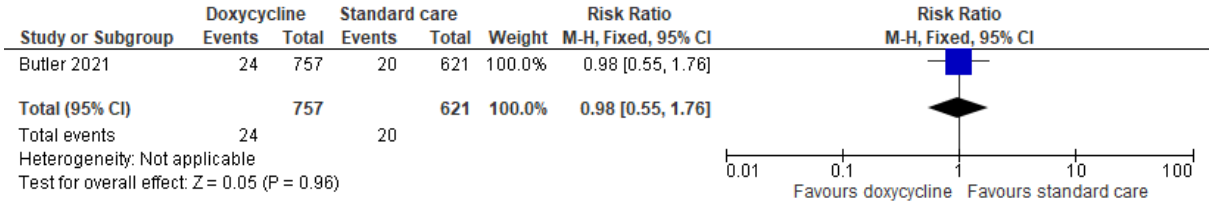
Mechanical ventilation within 28 days



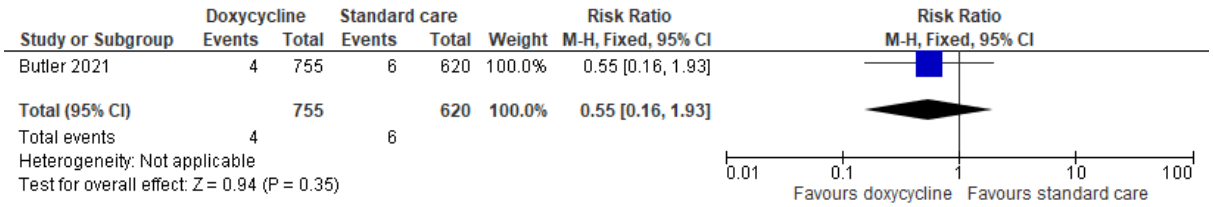
Significant adverse events



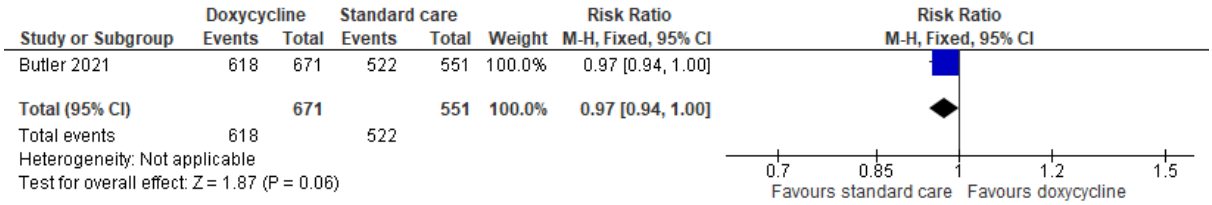
Oxygen administration within 28 days



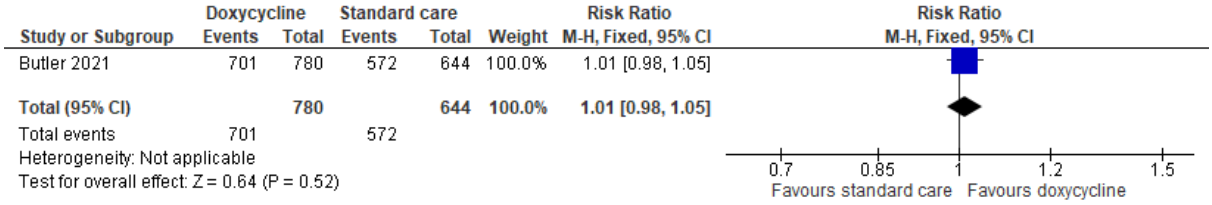
ICU admission within 28 days



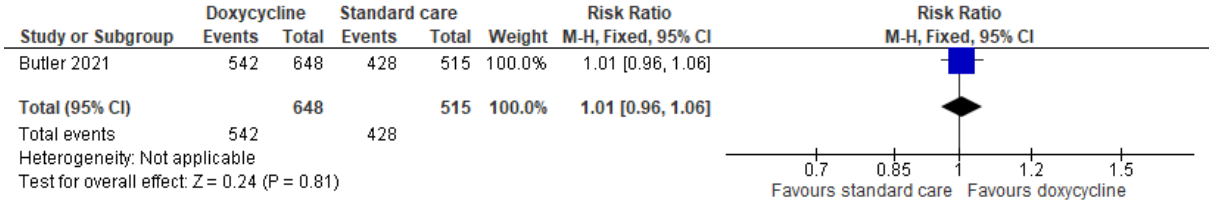
Alleviation of all symptoms within 28 days



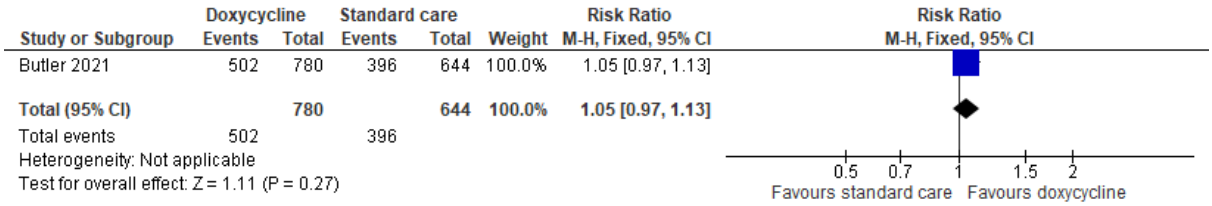
Initial reduction of severity of symptoms within 28 days



Sustained alleviation of all symptoms within 28 days



Sustained recovery within 28 days



Time to initial reduction of severity of symptoms

No forest plot. Data as reported in study.

Time of alleviation of all symptoms

No forest plot. Data as reported in study.

Time to first reported recovery

No forest plot. Data as reported in study.

Time to sustained recovery

No forest plot. Data as reported in study.

Appendix E: GRADE profiles

Doxycycline compared to standard care for COVID-19

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With standard care	With doxycycline		Risk with standard care	Risk difference with doxycycline
Hospitalisation/death (follow-up: 28 days)											
1728 (1 RCT)	not serious	not serious	not serious	serious[a]	none	Moderate	43/948 (4.5%)	41/780 (5.3%)	**OR 1.13** (0.73 to 1.74)	45 per 1,000	**7 more per 1,000** (from 11 fewer to 34 more)
Mechanical ventilation (follow-up: 28 days)											
1378 (1 RCT)	not serious	not serious	not serious	serious[b]	none	Moderate	5/621 (0.8%)	3/757 (0.4%)	**RR 0.49** (0.12 to 2.05)	8 per 1,000	**4 fewer per 1,000** (from 7 fewer to 8 more)
Significant adverse events											
1728 (1 RCT)	not serious	not serious	not serious	serious[c]	none	Moderate	5/948 (0.5%)	0/780 (0.0%)	**RR 0.11** (0.01 to 1.99)	5 per 1,000	**5 fewer per 1,000** (from 5 fewer to 5 more)
Oxygen administration (follow-up: 28 days)											
1378 (1 RCT)	not serious	not serious	not serious	serious[a]	none	Moderate	20/621 (3.2%)	24/757 (3.2%)	**RR 0.98** (0.55 to 1.76)	32 per 1,000	**1 fewer per 1,000** (from 14 fewer to 24 more)
ICU admission (follow-up: 28 days)											

Certainty assessment							Summary of findings				
1375 (1 RCT)	not serious	not serious	not serious	serious[b]	none	Moderate	6/620 (1.0%)	4/755 (0.5%)	**RR 0.55** (0.16 to 1.93)	10 per 1,000	**4 fewer per 1,000** (from 8 fewer to 9 more)
Alleviation of all symptoms (follow-up: 28 days)											
1222 (1 RCT)	not serious	not serious	not serious	not serious	none	High	522/551 (94.7%)	618/671 (92.1%)	**RR 0.97** (0.94 to 1.00)	947 per 1,000	**28 fewer per 1,000** (from 57 fewer to 0 fewer)
Initial reduction of severity of symptoms (follow-up: 28 days)											
1345 (1 RCT)	not serious	not serious	not serious	serious[a]	none	Moderate	572/644 (88.8%)	780/701 (111.3%)	**RR 1.01** (0.98 to 1.05)	888 per 1,000	**9 more per 1,000** (from 18 fewer to 44 more)
Sustained alleviation of all symptoms											
1163 (1 RCT)	not serious	not serious	not serious	serious[a]	none	Moderate	428/515 (83.1%)	542/648 (83.6%)	**RR 1.01** (0.96 to 1.06)	831 per 1,000	**8 more per 1,000** (from 33 fewer to 50 more)
Sustained recovery (follow-up: 28 days)											
1424 (1 RCT)	not serious	not serious	not serious	serious[a]	none	Moderate	396/644 (61.5%)	502/780 (64.4%)	**RR 1.05** (0.97 to 1.13)	615 per 1,000	**31 more per 1,000** (from 18 fewer to 80 more)
Time to initial reduction of severity of symptoms											
1424 (1 RCT)	not serious	not serious	not serious	serious[a]	none	Moderate	NA	NA	**HR 0.99** (0.88 to 1.11)	0 per 1,000	

Certainty assessment							Summary of findings				
Time to alleviation of all symptoms											
1222 (1 RCT)	not serious	not serious	not serious	serious[a]	none	Moderate	NA	NA	**HR 0.96** (0.86 to 1.09)	0 per 1,000	
Time to sustained alleviation of all symptoms											
1163 (1 RCT)	not serious	not serious	not serious	serious[a]	none	Moderate	NA	NA	**HR 1.03** (0.90 to 1.17)	0 per 1,000	
Time to first reported recovery											
1728 (1 RCT)	not serious	not serious	not serious	serious[a]	none	Moderate	NA	NA	**HR 1.04** (0.93 to 1.17)	0 per 1,000	
Time to sustained recovery											
1424 (1 RCT)	not serious	not serious	not serious	serious[a]	none	Moderate	NA	NA	**HR 1.00** (0.88 to 1.14)	0 per 1,000	

CI: confidence interval; **HR:** hazard Ratio; **RR:** risk ratio

Explanations

a. Only data from one study, due to confidence intervals crossing line of no effect
b. Wide confidence intervals, Low number of patients, Only data from one study, due to confidence intervals crossing line of no effect
c. Wide confidence intervals, Low number of patients, Only data from one study