NICE National Institute for Health and Care Excellence

Evidence review

# Acute use of non-steroidal anti-inflammatory drugs (NSAIDs) for people with or at risk of COVID-19

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This evidence review sets out the best available evidence on acute use of non-steroidal anti-inflammatory drugs (NSAIDs) for people with or at risk of COVID-19. It should be read in conjunction with the evidence summary, which gives the key messages.

Evidence review commissioned by NHS England

**Disclaimer**

The content of this evidence review was up-to-date on 24 March 2020. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information. For details on the date the searches for evidence were conducted see the search strategy.



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# Contents

## Background

As of 24 March 2020, the COVID-19 interactive web-based dashboard developed at Johns Hopkins University (Dong et al. 2020) had recorded that over 380,000 people globally have COVID-19. This disease is caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), which emerged in Wuhan, China in December 2019. Other diseases caused by coronaviruses include severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and the common cold.

COVID-19 manifests as a respiratory illness of widely varying clinical severity. The most common symptoms are fever and cough (Huang et al. 2019). At its most severe, it results in severe pneumonia needing mechanical ventilation, and can result in death. People with COVID-19 are offered best supportive care, with no established effective antiviral medication.

## Intervention

NSAIDs are a class of medicines that inhibit COX-1 and COX-2 enzymes leading to a reduction in production of prostaglandins. Prostaglandins mediate pain, fever, inflammation and swelling, and have a key role in gastric protection and haemostasis. Some NSAIDs are non-selective COX inhibitors (for example, ibuprofen, naproxen and indometacin). Others are selective COX-2 inhibitors (for example, etoricoxib and celecoxib), which more specifically target prostaglandins that mediate pain and inflammation.

Ibuprofen is available over the counter and is commonly used for pain and fever in acute illnesses in adults and children. It is also used in chronic inflammatory conditions such as rheumatoid arthritis and juvenile idiopathic arthritis. Many other NSAIDs are prescription-only medications, used for acute and chronic pain. The main adverse effects of over the counter NSAIDs (such as ibuprofen) include increased risk of gastric and oesophageal ulceration.

In 2012, the MHRA advised that some non-selective NSAIDs, such as diclofenac, are associated with increased cardiovascular risk compared with naproxen and low-dose ibuprofen (up to 1,200 mg per day). This increased risk is particularly apparent with long-term use of high doses and in people who are already at high risk of

cardiovascular disease. Further, in 2015, the MHRA advised that there is no increased risk of cardiovascular events seen with ibuprofen at doses up to 1,200 mg per day.

Ibuprofen use has been associated with increased severity of skin disease in varicella infections, including chickenpox and shingles; therefore NICE Clinical Knowledge Summaries advise against the use of ibuprofen in people with these conditions (Gould 2014).

## Clinical problem

COVID-19 is a rapidly evolving global pandemic, with countries facing different stages of the spread of disease. Therefore, there is limited published information about the disease course, vulnerable populations and mortality rate. The best available current data is from China, particularly Wuhan, where the virus first emerged. Data from this region suggest that people over the age of 70 years and those with comorbidities are most at risk of critical care admission and death. Children and young people appear to be less affected by the virus, with low numbers of deaths and critical care admissions in this age group (Wu et al. 2019).

On 14 March 2020, the French Health Ministry issued advice to avoid using NSAIDs to treat symptoms of COVID-19 after 4 people with this disease and no underlying health problems reportedly developed serious symptoms after using NSAIDs (Day 2020). This advice was based on a 2019 evaluation by the French National Agency for Medicines and Health Products Safety, which suggested that infection due to chickenpox (varicella) and some bacterial infections could be made worse by these medicines.

In response to these concerns, on 17 March 2020, the MHRA issued a Central alerting system (CAS) alert, in which the NHS England Medical Director, Professor Stephen Powis, gave interim advice that people with confirmed or suspected COVID-19 should use paracetamol in preference to NSAIDs, including ibuprofen. In the alert (CEM/CMO/2020/010), the NHS England Medical Director acknowledged there is limited evidence on the impact of NSAID use in COVID-19 and advised that the MHRA and NICE would review this topic.

## Objective

The purpose of this review is to assess the best available evidence to determine:

- If there is any increased risk of developing COVID-19 due to acute use of NSAIDs.
- If acute use of NSAIDs can lead to an increased risk of developing more severe symptoms of COVID-19.

## Methodology

A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) for this review was provided by NHS England for the topic (see the literature search terms section for more information). The research questions for this evidence review are:

1. In people taking NSAIDs acutely for acute respiratory tract infections, is there any evidence of being at greater risk of developing COVID-19 (or similar coronaviruses)?

2. In people who have confirmed or suspected COVID-19 (or a similar coronavirus), is there evidence that taking NSAIDs (acutely for the illness) is associated with greater severity of illness/symptoms?

3. Are there any subgroups of people taking NSAIDs acutely that may be at greater risk of developing COVID-19 (or similar coronaviruses)?

4. Are there any subgroups of people taking NSAIDs acutely that may be at greater risk of developing a more severe illness due to COVID-19?

This review does not consider people who are taking NSAIDs long-term for existing chronic conditions.

The searches for evidence to support using NSAIDs for people with or at risk of COVID-19 were undertaken by NICE Guidance Information Services. Results from the literature searches were screened using their titles and abstracts for relevance against the criteria from the PICO, by 2 reviewers. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the PICO inclusion criteria for this evidence review. More information can be found in the sections on search strategy and evidence selection.

The evidence review was undertaken following NHS England's 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2016) and the NICE evidence summary: process guide (2017).

## Summary of included studies

No relevant papers were identified in the searches undertaken for this evidence review.

Details of the excluded studies are listed in the section on evidence selection.

## Effectiveness and safety

No study results were available to determine if there is any increased risk of developing COVID-19 due to acute use of NSAIDs, or if acute use of NSAIDs can lead to an increased risk of developing more severe symptoms of COVID-19.

## Discussion and limitations of the evidence

No evidence was found to determine whether using NSAIDs acutely is related to increased risk of developing COVID-19 or increased risk of a more severe illness. The advice by the French Health Minister to avoid NSAIDs was based on a French national pharmacovigilance evaluation of the 2 NSAIDs most commonly used for mild to moderate pain and fever in France (ibuprofen and ketoprofen). The evaluation was undertaken in 2018 following reports of serious infectious complications with these medicines, and limited results were published in 2019.

The French evaluation found that, since 2000, 337 cases of serious infectious complications were reported with ibuprofen in children or adults without risk factors or comorbidities, and 49 cases were reported with ketoprofen. Infectious complications included severe infections of the skin and soft tissues (for example, dermo-hypodermitis or necrotising fasciitis), sepsis, pulmonary infections (such as pneumonia complicated by abscess or pleurisy), neurological infections (such as empyema or brain abscess), hospitalisations and death. The evaluation also showed that NSAIDs were still being used for chickenpox. NSAIDs are already known to increase the risk of skin infections such as necrotising fasciitis in people with chickenpox.

Infectious complications (mainly Streptococcus or Pneumococcus) were seen after short treatment periods (2 to 3 days), when an NSAID was used alone or in combination with an antibiotic, and when the NSAID was prescribed or bought over the counter. Indications for the NSAID included fever, skin bites and reactions, respiratory symptoms (such as coughs) and ear, nose and throat symptoms (such as dysphagia and otitis).

The French National Agency for the Safety of Medicines and Health Products (ANSM) concluded that analysis of these cases and data from the literature (experimental studies and pharmacoepidemiology studies) suggest that these infections, especially Streptococcus, might be aggravated by ibuprofen and ketoprofen. ANSM shared the results with the European Medicines Agency (EMA) so that a wider analysis could be undertaken.

In May 2019, the EMA's safety committee (the Pharmacovigilance Risk Assessment Committee [PRAC]) started a review of ibuprofen and ketoprofen. It noted that the product information of some NSAIDs already contains warnings that their anti-inflammatory effects may hide the symptoms of a worsening infection. Nevertheless, the PRAC is reviewing all available data to see if any additional measures are required, and the EMA will provide further information as necessary and once the review is concluded.

On 18 March 2020, the EMA issued a press release stating that there is currently no scientific evidence establishing a link between ibuprofen and worsening of COVID-19. The EMA is monitoring the situation closely and will review any new information that becomes available on this issue in the context of the pandemic.

The NHS England Medical Director issued a CAS alert on 17 March 2020 following the French advice to avoid NSAIDs, which reportedly came after 4 people with COVID-19 and no underlying health problems developed serious symptoms after using NSAIDs (Day 2020). The advice from the French Health Minister was based on the 2019 evaluation by the ANSM. The NHS England Medical Director noted that UK authorities have seen only provisional information on the adverse effects of NSAIDs reported in France, and that the full data have not yet been published.

In the CAS alert, the NHS England Medical Director said there is currently no literature on the impact of NSAID use in COVID-19, but there appears to be some evidence (from experimental studies in SARS 1) that there may be an adverse impact on pneumonia. In addition, he noted that some literature suggests NSAIDs may increase complications from simple acute respiratory infections or slow recovery. The Centre for Evidence-Based Medicine (CEBM) found that research evidence in coronavirus is currently lacking and, instead, assessed the evidence for NSAIDs in acute respiratory infection as part of its service to support healthcare professionals during the current COVID-19 pandemic.

The CEBM found 5 studies in which NSAIDs were associated with worsening outcomes (including hospitalisation and pneumonia or pleuropulmonary complications) in acute respiratory infections (not including COVID-19). All 5 studies suggested that NSAIDs worsen outcomes. However, these were all observational studies and, as the authors pointed out, are difficult to interpret because they could have been subject to confounding by indication. People with more severe disease and more severe symptoms may take more NSAIDs. Consequently, this may have been an association with, and not necessarily a cause of, people developing more severe disease. Nevertheless, the CEBM concluded that NSAIDs do not significantly reduce total symptoms or duration of respiratory infections. Note that the duration of treatment (acute or chronic) with NSAIDs in the studies is unclear from the review.

The consensus opinion of several scientists and senior doctors expressed in a news article in the BMJ (Day 2020). supported the French Health Minister's view that people showing symptoms of COVID-19 should use paracetamol (acetaminophen) in preference to ibuprofen. The article referenced 2 randomised controlled trials (RCTs) that assessed treatments (including ibuprofen) in respiratory tract infections.

The first of these RCTs (Little et al. 2013) assessed strategies for advice on various treatments for respiratory tract infections in 889 adults and children. It found that reconsultations with new or unresolved symptoms or complications were documented in 12% of those advised to take paracetamol compared with 20% of those advised to take ibuprofen (p=0.012, statistically significant). However, in a subgroup of people with lower respiratory tract infections, ibuprofen reduced

symptom severity compared with paracetamol (n=113, p=0.04, statistically significant).

The second RCT (Little et al. 2016) in 1,772 adults assessed an internet-delivered intervention providing advice to manage respiratory tract infections with no such intervention. The study found that the duration of more severe symptoms was 0.52 days longer in the intervention group compared with the control group (p=0.026, statistically significant). The authors noted that this could either have been a chance finding or because participants were more aware of symptoms. However, they also considered that, by strongly encouraging the use of not only paracetamol but also ibuprofen, the internet-delivered intervention may have significantly increased ibuprofen use, which may have prolonged illness.

The results of these 2 RCTs should not be taken in isolation. No formal searches were undertaken in this evidence review for acute use of NSAIDs for typical acute respiratory tract infections because the scope only covered COVID-19 and similar coronaviruses. Also, evidence for using NSAIDs for typical acute respiratory tract infections (such as these 2 RCTs) has not been critically appraised.

In another review, the CEBM considered whether suppressing fever in acute respiratory tract infections affects outcomes. The review found that ibuprofen has been shown to reduce fever, tachycardia and oxygen consumption, but not prevent shock or acute respiratory distress syndrome, nor improve survival (1 RCT, n=455). Most paracetamol studies reported lower body temperature; however, reductions were modest. The CEBM concluded that the current evidence does not support routine antipyretic administration to treat fever in acute respiratory infections and COVID-19.

An experimental study of COVID-19 using DNA from 5 people (Zhou et al. 2020) found that SARS-CoV-2, like other SARS viruses, is able to use angiotensin converting enzyme 2 (ACE2) protein as a receptor to enter cells that express ACE2. Correspondence in the Lancet Respiratory Medicine (Fang et al. 2020) hypothesised that treatment with ACE2-stimulating drugs (which the article says includes ibuprofen but does not mention other NSAIDs) increases the risk of developing severe and fatal COVID-19. It is plausible that upregulating ACE2 could increase a person's risk

of developing COVID-19. However, a reduction in ACE2 has been shown to be a factor in more severe disease or acute lung injury in SARS (Zhang et al. 2020), and further research is needed to test this theory in clinical practice.

## Likely place in therapy

NHS England has developed a commissioning policy for acute use of NSAIDs for people with or at risk of COVID-19.

## Conclusion

At this time, policy decisions on whether NSAIDs should be used for treating symptoms of COVID-19 will need to take into account data extrapolated from studies involving the use of NSAIDs for other acute respiratory tract infections, together with pharmacoepidemiological studies.

The available evidence suggests that, although the anti-inflammatory effects of NSAIDs reduce acute symptoms (such as fever), they may either have no effect on, or worsen, long-term outcomes, possibly by masking symptoms of worsening acute respiratory tract infection. Further evidence is needed to confirm this, and to determine whether these results also apply to infections such as COVID-19.

## References


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Day M (2020) Covid-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. BMJ 368 https://doi.org/10.1136/bmj.m1086

Dong E, Du H, Gardner L (2020) An interactive web-based dashboard to track COVID-19 in real time. Lancet Infectious Diseases https://doi.org/10.1016/S1473-3099(20)30120-1

EMA (2020) EMA gives advice on the use of non-steroidal anti-inflammatories for COVID-19.

Fang l, Karakiulakis G, Roth M (2020) Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med https://doi.org/10.1016/PII

Gould D (2014) Varicella zoster virus: chickenpox and shingles. Nursing Standard 28(33): 52–8

Heneghan C, Brassey J (2020) NSAIDs in Acute Respiratory Infection

Huang C, Wang Y, Li X et al. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395(10223): 497–506

Little P, Moore M, Kelly J et al. (2013) Ibuprofen, paracetamol, and steam for patients with respiratory tract infections in primary care: pragmatic randomised factorial trial. BMJ 347: f6041

Little P, Stuart B, Andreou P et al. (2016) Primary care randomised controlled trial of a tailored interactive website for the self-management of respiratory infections (Internet Doctor). BMJ open 6(4): e009769

MHRA (2012) Non-steroidal anti-inflammatory drugs (NSAIDs): cardiovascular risks. Drug Safety Update vol 6, issue 3: S1

MHRA (2015) High-dose ibuprofen (≥2400mg/day): small increase in cardiovascular risk. Drug Safety Update Volume 8, issue 11

NHS England Medical Director (2020) Novel coronavirus - anti-inflammatory medications. CEM/CMO/2020/010

NICE (2018) Clinical knowledge summary: chickenpox

NICE (2019) Clinical knowledge summary: NSAIDs - prescribing issues

Park S, Brassey J, Heneghan C et al. (2020) Managing Fever in adults with possible or confirmed COVID-19 in Primary Care

Wu Z, McGoogan JM (2020) Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. JAMA doi:10.1001/jama.2020.2648

# Appendices

## *Appendix A: Literature search terms*

| Search strategy | |
|---|---|
| P – Patients / Population<br>Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered? | Related to research questions 1 and 3:<br>People without COVID-191 that are taking NSAIDs acutely<br>Related to research questions 2 and 4:<br>People with suspected or confirmed COVID-192 that are taking NSAIDs acutely<br>Subgroups:<br>Over 70 years<br>Children<br>Immunocompromised<br>Comorbidities (such as hypertension, diabetes mellitus)<br>No comorbidities<br>Disease type (particularly SARS-CoV-2 (COVID-19) and others such as severe acute respiratory syndrome (SARS-CoV-1), Middle East respiratory syndrome (MERS)). |
| I – Intervention<br>Which intervention, treatment or approach should be used? | Oral NSAIDs: aceclofenac, acemetacin, aspirin, celecoxib, dexibuprofen, dexketoprofen, diclofenac potassium, diclofenac sodium, etodolac, etoricoxib, felbinac, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, mefenamic acid, meloxicam, nabumetone, naproxen, piroxicam, sulindac, tenoxicam and tiaprofenic acid. |
| C – Comparison<br>What is/are the main alternative/s to compare with the intervention being considered? | No comparator |
| O – Outcomes<br>What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission | Critical to decision-making:<br>Mortality<br>Requirement for critical care admission<br>Requirement for mechanical/non-invasive ventilation<br>Incidence of COVID-19 (or similar coronaviruses)<br><br>Important to decision-making:<br>Requirement for admission to hospital |

[1] There may be limited evidence related to Covid-19. Evidence related to other coronaviruses, such as severe acute respiratory syndrome (SARS-CoV-1) or Middle East respiratory syndrome (MERS-CoV) should also be considered.
[2] There may be limited evidence related to Covid-19. Evidence related to other coronaviruses, such as severe acute respiratory syndrome (SARS-CoV-1) or Middle East respiratory syndrome (MERS-CoV) should also be considered.

| | |
|---|---|
| | Length of stay in critical care<br>Length of stay in hospital<br>Duration of illness/symptoms3<br>Severity of illness/symptoms<br>Complications of disease (such as pulmonary and renal complications) |
| Assumptions / limits applied to search | |
| Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered. If no case series are identified, case reports can be considered<br>English only, human studies only, all ages, 2000-2020 | |

[3] Symptoms and illness defined as the following: critical illness – lung failure, septic shock, organ failure and risk of death; severe symptoms – dyspnoea; mild symptoms – fever and cough

## *Appendix B: Search strategy*

### Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor: [Coronavirus] explode all trees
#2 ((corona* or corono*) near/1 (virus* or viral* or virinae*)):ti,ab,kw
#3 (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or "SARS-CoV-1" or "SARSCoV-1" or "SARSCoV1" or "SARS-CoV1" or MERS-CoV or "MERS-CoV" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*):ti,ab,kw
#4 (((respiratory* near/2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") near/10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)):ti,ab,kw
#5 ((outbreak* or wildlife* or pandemic* or epidemic*) near/1 (China* or Chinese* or Huanan*)):ti,ab,kw
#6 MeSH descriptor: [Middle East Respiratory Syndrome Coronavirus] this term only
#7 "severe acute respiratory syndrome*" or "middle east respiratory syndrome*":ti,ab,kw
#8 {or #1-#7}
#9 MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees
#10 ((nonsteroid* or non steroid*) near/3 (anti inflammator* or antiinflammator*)):ti,ab,kw
#11 nsaid*:ti,ab,kw
#12 (acetylsalicylic acid or aspirin* or ibuprofen* or acemetacin* or ebufac* or celecoxib* or etoricoxib* or diclofenac* or etodolac* or felbinac* or aceclofenac* or dexibuprofen* or etodolac* or indometacin* or naproxen* or nurofen* or fenoprofen* or flurbiprofen* or ketoprofen* or tiaprofenic* or dexketoprofen* or Mefenamic acid or Meloxicam* or Nabumetone* or Piroxicam* or Sulindac* or Tenoxicam*):ti,ab,kw
#13 {or #9-#12}
#14 #8 and #13

### Embase

1 exp Coronavirinae/ (10789)
2 Middle East respiratory syndrome/ (784)
3 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. (498)
4 (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or "SARS-CoV-1" or "SARSCoV-1" or "SARSCoV1" or "SARS-CoV1" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or MERS-CoV or "MERS-CoV" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ti,ab,kw. (20235)

5 (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (545)
6 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw. (74)
7 ("severe acute respiratory syndrome*" or "middle east respiratory syndrome*").ti,ab,kw. (6585)
8 or/1-7 (27244)
9 exp nonsteroid antiinflammatory agent/ (723805)
10 ibuprofen derivative/ (201)
11 (acetylsalicylic acid or aspirin* or ibuprofen* or acemetacin* or ebufac* or celecoxib* or etoricoxib* or diclofenac* or etodolac* or felbinac* or aceclofenac* or dexibuprofen* or etodolac* or indometacin* or naproxen* or nurofen* or fenoprofen* or flurbiprofen* or ketoprofen* or tiaprofenic* or dexketoprofen* or Mefenamic acid or Meloxicam* or Nabumetone* or Piroxicam* or Sulindac* or Tenoxicam*).tw. (187004)
12 or/9-11 (735733)
13 8 and 12 (136)

**MEDLINE ALL**

1 exp coronavirus/ (11252)
2 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. (604)
3 (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or "SARS-CoV-1" or "SARSCoV-1" or "SARSCoV1" or "SARS-CoV1" or MERS-CoV or "MERS-CoV" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ti,ab,kw. (17164)
4 (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (451)
5 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw. (165)
6 Middle East Respiratory Syndrome Coronavirus/ (956)
7 ("severe acute respiratory syndrome*" or "middle east respiratory syndrome*").ti,ab,kw. (6047)
8 or/1-7 (23819)
9 exp Anti-Inflammatory Agents, Non-Steroidal/ (195795)
10 ((nonsteroid* or non steroid*) adj3 (anti inflammator* or antiinflammator*)).tw. (38662)
11 nsaid*.tw. (24464)
12 (acetylsalicylic acid or aspirin* or ibuprofen* or acemetacin* or ebufac* or celecoxib* or etoricoxib* or diclofenac* or etodolac* or felbinac* or aceclofenac* or dexibuprofen* or etodolac* or indometacin* or naproxen* or nurofen* or fenoprofen* or flurbiprofen* or ketoprofen* or tiaprofenic* or dexketoprofen* or Mefenamic acid or Meloxicam* or Nabumetone* or Piroxicam* or Sulindac* or Tenoxicam*).tw. (97797)

13 or/9-12 (244885)
14 8 and 13 (37)

## *Appendix C: Evidence selection*

A literature search was conducted which identified 156 references (see search strategy for full details). These references were screened using their titles and abstracts and 13 references were obtained and assessed for relevance. Of these, none are included in the evidence summary.

The excluded references are listed in the following table. All were excluded because they do not look at outcomes in people with COVID-19 (or a similar coronavirus) treated with NSAIDs.

| **Study reference** |
|---|
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