NICE National Institute for Health and Care Excellence

Evidence review

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

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May 2020

This evidence review sets out the best available evidence on long-term 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.

Commissioned by NHS England

Disclaimer

The content of this evidence review was up-to-date on 20 April 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 20 April 2020, the COVID-19 interactive web-based dashboard developed at Johns Hopkins University (Dong et al. 2020) stated that there have been over 2,411,000 confirmed cases of COVID-19 globally. Around 165,000 people had reportedly died by that date and 629,000 have recovered.

COVID-19 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

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of medicines that inhibit cycloxygenase-1 (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.

Some NSAIDs, such as ibuprofen, are available over the counter and are commonly used for pain and fever in acute illnesses in adults and children. Many other NSAIDs are prescription-only medications, used for acute and chronic pain. Indications for long-term use of NSAIDs include ankylosing spondylitis, rheumatoid arthritis, osteoarthritis, juvenile arthritis and pain in sickle cell disease. For the purposes of this evidence review, long-term use of NSAIDs is defined as a regular, moderate dose of NSAIDs for at least 2 weeks, normally for chronic conditions.

The main adverse effects of NSAIDs 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.

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. Studies on COVID-19 are limited mainly to observational studies from China, particularly Wuhan, where the virus first emerged. Data from this region suggest that older age and presence of comorbidities are the main risk factors for dying in hospital (Zhou et al. 2020). 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, NHS England issued a Central Alerting System (CAS) alert, in which the NHS England Medical Director, Professor Stephen Powis, gave interim advice that people who are currently on NSAIDs for medical reasons (such as arthritis) should not stop them. 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.

NICE has produced an evidence review on acute NSAID use for COVID-19, which informed a subsequent NHS England and NHS Improvement policy statement. The policy states that, when patients, carers or healthcare professionals are starting treatment for fever and/or pain in adults or children with confirmed or suspected COVID-19, all treatment options should be considered and selected based on the greatest benefit compared to potential harms using each medicine's product information (see the NICE COVID-19 guideline on managing symptoms (including at end of life) in the community).

A proportion of people taking long-term NSAIDs for other conditions may be at higher risk of developing COVID-19 or more severe COVID-19 because of their chronic condition or concomitant medication; for example, people with rheumatoid arthritis taking immunosuppressants. This evidence review considers the best available evidence on whether long-term use of NSAIDs (including high anti-inflammatory doses of aspirin) is an independent risk factor for developing COVID-19 or for developing more severe COVID-19.

Objective

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

1. If long-term use of NSAIDs is associated with an increased risk of developing COVID-19.
2. If long-term use of NSAIDs is associated with an increased risk of developing more severe 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 research questions section for more information). The research questions for this evidence review are:

1. In people taking NSAIDs long-term is there evidence of being at greater risk of developing COVID-19?

2. Are there any subgroups of people taking NSAIDs long-term that may be at greater risk of developing COVID-19?

3. In people who have confirmed or suspected COVID-19, is there evidence that taking NSAIDs long-term is associated with more severe COVID-19?

4. Are there any subgroups of people taking NSAIDs long-term that may be at greater risk of developing more severe COVID-19?

The searches for evidence on NSAIDs use and 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 a modified version of the NHS England process for developing evidence reviews.

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 studies were found to determine if there is any increased risk of developing COVID-19 due to long-term use of NSAIDs, or if long-term use of NSAIDs can lead to an increased risk of developing more severe COVID-19.

Discussion and limitations of the evidence

No evidence was found to determine whether using NSAIDs long-term is related to an increased risk of developing COVID-19 or increased risk of more severe COVID-19.

Most of the published articles that discuss using NSAIDs in people with COVID-19 relate to short-term use for treating pain and fever in people with infections, which has been discussed in another evidence review.

The advice by the French Health Minister to avoid NSAIDs on 14 March 2020 was based on an evaluation by the French National Agency for Medicines and Health Products Safety, which considered 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. Indications for NSAIDs were short-term infections, including fever, skin bites and reactions, respiratory symptoms (such as coughs) and ear, nose and throat symptoms (such as dysphagia and otitis).

In 2019, the French National Agency for the Safety of Medicines and Health Products concluded that analysis of these cases and data from the literature (experimental studies and pharmacoepidemiology studies) suggest that these infections might be aggravated by ibuprofen and ketoprofen. The French Agency shared the results with the European Medicines Agency (EMA) so that a wider analysis could be undertaken.

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. On 14 April 2020, the MHRA issued a similar statement, concluding there is currently insufficient evidence to establish a link between use of ibuprofen and susceptibility to contracting COVID-19 or the worsening of its symptoms..

Several scientists and senior doctors have expressed their views in the medical press about whether NSAIDs should be used or not in people with COVID-19, with all agreeing that the evidence is uncertain in this population (Day 2020, FitzGerald 2020 and Little 2020). Their opinions are generally based on studies in which NSAIDs were used to treat symptoms of pain and fever in people with other infections (not COVID-19), or on experimental studies.

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. The MHRA also stated that NSAIDs (including COX-2 inhibitors) may rarely precipitate renal failure, and vulnerable (particularly elderly) people may be at increased risk.

Gastrointestinal, respiratory, cardiovascular and renal adverse effects are listed among the possible adverse effects of NSAIDs in the BNF. COVID-19 may also lead to respiratory, cardiovascular and renal complications (BMJ Best Practice: complications). In addition, certain comorbidities (such as diabetes, hypertension, cardiovascular disease and chronic respiratory disease) increase the risk of more severe COVID-19 (The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team 2020).

A recent BMJ Editorial notes that NSAIDs can cause nephrotoxicity, which is more likely in the patient groups most likely to be seriously affected by COVID-19 (for example, older people with comorbidities) and is exacerbated by fever and dehydration (Little 2020).

Another article considers that, although NSAIDs can have adverse effects and may not be first choice for managing symptoms of COVID-19 in people with cardiovascular, renal or gastrointestinal problems, people with chronic pain (without COVID-19) and already taking NSAIDs should continue with them rather than switching to opiates until there is robust evidence suggesting otherwise (FitzGerald 2020). The author notes that, because older people appear to be the predominant at-risk group for severe COVID-19, an association between NSAIDs and the disease may merely reflect reverse causality (that is, the infection makes the person more susceptible to adverse effects of NSAIDs; for example, by causing dehydration and increasing the risk of nephrotoxicity).

The NICE COVID-19 rapid guideline on rheumatological autoimmune, inflammatory and metabolic bone disorders recommends that people taking an NSAID for a long-term condition such as rheumatoid arthritis should be advised that it does not need to be stopped.

Conclusion

No evidence was found to determine whether using NSAIDs long-term is related to increased risk of developing COVID-19 or increased risk of more severe COVID-19,

and there is no evidence to suggest that people taking NSAIDs for a long-term condition should be advised to stop treatment. Stopping or switching NSAID treatment could have a negative impact on some people.

Clinicians should follow advice in the BNF and the NICE Clinical Knowledge Summary on issues around prescribing NSAIDs. When considering an NSAID, individual risk factors for adverse effects should be considered, including any contraindications, drug interactions, medical history, and any monitoring requirements. The lowest effective dose of an NSAID should be used for the shortest period of time required to control symptoms and the need for long-term treatment should be reviewed periodically.

At this time, policy decisions on whether NSAIDs should be used long-term in people with confirmed or suspected COVID-19 will need to take into account the risk of adverse effects of NSAIDs, the risk of complications of COVID-19, and the presence of comorbidities that increase the risk of more severe COVID-19.

References

ANSM (2019) Anti-inflammatoires non stéroïdiens (AINS) et complications infectieuses graves - Point d'Information

BMJ Best Practice 2020 Coronavirus disease 2019 (COVID-19)

Day M (2020) Covid-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. BMJ 368: 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.

FitzGerald GA (2020) Misguided drug advice for COVID-19. Science 367 (6485): 1434

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 (2020) Non-steroidal anti-inflammatory drugs and covid-19. BMJ 368: m1185

MHRA (2009) Non-steroidal anti-inflammatory drugs (NSAIDs): reminder on renal failure and impairment. Drug Safety Update vol 2 issue 10: 4

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 (2019) Clinical knowledge summary: NSAIDs - prescribing issues

NICE (2020) COVID-19 rapid guideline: rheumatological autoimmune, inflammatory and metabolic bone disorders NG167

The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team (2020) The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020. China CDC Weekly 2(8): 113–122

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

Zhou F, Yu T, Du R et al. (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395: 1054–62

Appendices

Appendix A: Research questions

Research questions

1. In people taking NSAIDs long-term is there evidence of being at greater risk of developing COVID-19?
2. Are there any subgroups of people taking NSAIDs long-term that may be at greater risk of developing COVID-19?
3. In people who have confirmed or suspected COVID-19, is there evidence that taking NSAIDs long-term is associated with more severe COVID-19?
4. Are there any subgroups of people taking NSAIDs long-term that may be at greater risk of developing more severe COVID-19?

Population, Intervention, Comparator and Outcomes (PICO) table

P – Population and Indication	1. People without COVID-19[1] taking NSAIDs long-term (related to research questions 1 and 2 above) 2. People with suspected or confirmed COVID-19[2] taking NSAIDs long-term (related to research questions 3 and 4 above) Subgroups: • Over 70 years • Children • Immunocompromised • Comorbidities (such as rheumatoid arthritis, obesity) • Disease type (particularly SARS-CoV-2 (COVID-19) and other coronavirus diseases such as severe acute respiratory syndrome (SARS-CoV-1), Middle East respiratory syndrome (MERS)).
I – Intervention	Long-term[3] oral NSAIDs: aceclofenac, acemetacin, 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, aspirin (high dose).
C – Comparator(s)	No comparator
O – Outcomes	**Critical to decision-making:** • Mortality • Requirement for critical care admission • Requirement for mechanical/non-invasive ventilation **Important to decision-making:** • Requirement for admission to hospital • Length of stay in critical care

	• Length of stay in hospital • Duration of disease/symptoms[4] • Severity of disease/symptoms • Complications of disease (such as pulmonary and renal complications)
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, observational studies including case series. If no higher-level quality evidence is found, case reports can be considered.
Language	English only
Patients	Human studies only in the review. Evidence from in vitro and animal studies can be considered for the background (rationale for theories)
Age	All ages
Date limits	2000-2020
Exclusion criteria	-
Publication type	None
Study design	None
	Notes [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. [3] Regular moderate dose of NSAIDs for at least 2 weeks or more, normally for chronic conditions. For the purpose of this policy development and review, the use of NSAIDs would need to be active (i.e. in the 2 weeks leading up to the potential/confirmed COVID-19 illness). [4] 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)

ID Search Hits
#1 MeSH descriptor: [Coronavirus] explode all trees 11
#2 MeSH descriptor: [Coronavirus Infections] explode all trees 38
#3 ((corona* or corono*) near/1 (virus* or viral* or virinae*)):ti,ab,kw 14
#4 (coronavirus* or coronovirus* or coronavirinae* or CoV or HCoV*):ti,ab,kw 196
#5 ("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 "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 Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese* or SARS2 or "SARS-2" or SARScoronavirus2 or "SARS-coronavirus-2" or "SARScoronavirus 2" or "SARS coronavirus2" or SARScoronovirus2 or "SARS-coronovirus-2" or "SARScoronovirus 2" or "SARS coronovirus2"):ti,ab,kw 30
#6 (((respiratory* near/2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*" or pneumonia*) near/10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)):ti,ab,kw 134
#7 ((outbreak* or wildlife* or pandemic* or epidemic*) near/1 (China* or Chinese* or Huanan*)):ti,ab,kw 1
#8 MeSH descriptor: [Middle East Respiratory Syndrome Coronavirus] explode all trees 1
#9 ("middle east respiratory syndrome*" or "middle eastern respiratory syndrome*" or MERSCoV or "MERS-CoV" or MERS):ti,ab,kw 38
#10 ("severe acute respiratory syndrome*" or SARS):ti,ab,kw 172
#11 ("SARS-CoV-1" or "SARSCoV-1" or "SARSCoV1" or "SARS-CoV1" or SARSCoV or SARS-CoV or SARS1 or "SARS-1" or SARScoronavirus1 or "SARS-coronavirus-1" or "SARScoronavirus 1" or "SARS coronavirus1" or SARScoronovirus1 or "SARS-coronovirus-1" or "SARScoronovirus 1" or "SARS coronovirus1"):ti,ab,kw 18
#12 {or #1-#11} 480
#13 MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees 7519
#14 ((nonsteroid* or non steroid*) near/3 (anti inflammator* or antiinflammator*)):ti,ab,kw 13363
#15 nsaid*:ti,ab,kw 6306
#16 (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 33051
#17 {or #13-#16} 42442
#18 #12 and #17 with Cochrane Library publication date Between Mar 2020 and Apr 2020, in Trials 0

Cochrane Database of Systematic Reviews (CDSR)

Before doing new searches check the Cochrane special collections for curated resources:
Coronavirus (COVID-19): infection control and prevention measures
Assembles Cochrane Reviews identified as most directly relevant to the prevention of infection.
https://www.cochranelibrary.com/collections/doi/SC000040/full
Coronavirus (COVID-19): evidence relevant to critical care
Assembles Cochrane Reviews identified as most directly relevant to the management of people hospitalized with severe acute respiratory infections.
https://www.cochranelibrary.com/collections/doi/SC000039/full

Embase

1 exp Coronavirinae/ (11728)
2 exp Coronavirus infection/ (11514)
3 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. (551)
4 (coronavirus* or coronovirus* or coronavirinae* or CoV or HCoV*).ti,ab,kw. (15771)
5 ("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 "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 Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese* or SARS2 or "SARS-2" or SARScoronavirus2 or "SARS-coronavirus-2" or "SARScoronavirus 2" or "SARS coronavirus2" or SARScoronovirus2 or "SARS-coronovirus-2" or "SARScoronovirus 2" or "SARS coronovirus2").ti,ab,kw. (1920)
6 (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*" or pneumonia*) adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. (1682)
7 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw. (80)
8 Middle East respiratory syndrome/ (832)
9 ("middle east respiratory syndrome*" or "middle eastern respiratory syndrome*" or MERSCoV or "MERS-CoV" or MERS).ti,ab,kw. (4974)
10 ("severe acute respiratory syndrome*" or SARS).ti,ab,kw. (11062)
11 ("SARS-CoV-1" or "SARSCoV-1" or "SARSCoV1" or "SARS-CoV1" or SARSCoV or SARS-CoV or SARS1 or "SARS-1" or SARScoronavirus1 or "SARS-coronavirus-1" or "SARScoronavirus 1" or "SARS coronavirus1" or SARScoronovirus1 or "SARS-coronovirus-1" or "SARScoronovirus 1" or "SARS coronovirus1").ti,ab,kw. (3062)
12 or/1-11 (33427)
13 exp nonsteroid antiinflammatory agent/ (726173)
14 ibuprofen derivative/ (202)
15 nsaid*.tw. (42785)
16 (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. (187601)
17 or/13-16 (743728)
18 12 and 17 (200)
19 (202003* or 202004*).dc. (230374)
20 18 and 19 (7)

MEDLINE ALL

1 exp coronavirus/ (11594)
2 exp Coronavirus Infections/ (9915)
3 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw,kf. (680)
4 (coronavirus* or coronovirus* or coronavirinae* or CoV or HCoV*).ti,ab,kw,kf. (14020)
5 ("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 "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 Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese* or SARS2 or "SARS-2" or SARScoronavirus2 or "SARS-coronavirus-2" or "SARScoronavirus 2" or "SARS coronavirus2" or SARScoronovirus2 or "SARS-coronovirus-2" or "SARScoronovirus 2" or "SARS coronovirus2").ti,ab,kw,kf. (2582)
6 (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*" or pneumonia*) adj10 (Wuhan* or Hubei* or China* or Chinese*

or Huanan*)).ti,ab,kw,kf. (1454)
7 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (Wuhan* or Hubei or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (192)
8 Middle East Respiratory Syndrome Coronavirus/ (986)
9 ("middle east respiratory syndrome*" or "middle eastern respiratory syndrome*" or MERSCoV or "MERS-CoV" or MERS).ti,ab,kw,kf. (4490)
10 ("severe acute respiratory syndrome*" or SARS).ti,ab,kw,kf. (10032)
11 ("SARS-CoV-1" or "SARSCoV-1" or "SARSCoV1" or "SARS-CoV1" or SARSCoV or SARS-CoV or SARS1 or "SARS-1" or SARScoronavirus1 or "SARS-coronavirus-1" or "SARScoronavirus 1" or "SARS coronavirus1" or SARScoronovirus1 or "SARS-coronovirus-1" or "SARScoronovirus 1" or "SARS coronovirus1").ti,ab,kw,kf. (3017)
12 or/1-11 (28972)
13 exp Anti-Inflammatory Agents, Non-Steroidal/ (196040)
14 ((nonsteroid* or non steroid*) adj3 (anti inflammator* or antiinflammator*)).tw. (38719)
15 nsaid*.tw. (24500)
16 (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. (97982)
17 or/13-16 (245257)
18 12 and 17 (56)
19 (202003* or 202004*).ed. (94139)
20 (202003* or 202004*).dt. (129050)
21 19 or 20 (219218)
22 18 and 21 (6)

MEDLINE Epubs and Daily

1 exp coronavirus/ (0)
2 exp Coronavirus Infections/ (0)
3 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw,kf. (100)
4 (coronavirus* or coronovirus* or coronavirinae* or CoV or HCoV*).ti,ab,kw,kf. (1279)
5 ("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 "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 Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese* or SARS2 or "SARS-2" or SARScoronavirus2 or "SARS-coronavirus-2" or "SARScoronavirus 2" or "SARS coronavirus2" or SARScoronovirus2 or "SARS-coronovirus-2" or "SARScoronovirus 2" or "SARS coronovirus2").ti,ab,kw,kf. (1602)
6 (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*" or pneumonia*) adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (129)
7 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (Wuhan* or Hubei or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (23)
8 Middle East Respiratory Syndrome Coronavirus/ (0)
9 ("middle east respiratory syndrome*" or "middle eastern respiratory syndrome*" or MERSCoV or "MERS-CoV" or MERS).ti,ab,kw,kf. (143)
10 ("severe acute respiratory syndrome*" or SARS).ti,ab,kw,kf. (644)
11 ("SARS-CoV-1" or "SARSCoV-1" or "SARSCoV1" or "SARS-CoV1" or SARSCoV or SARS-CoV or SARS1 or "SARS-1" or SARScoronavirus1 or "SARS-coronavirus-1" or "SARScoronavirus 1" or "SARS coronavirus1" or SARScoronovirus1 or "SARS-coronovirus-1" or "SARScoronovirus 1" or "SARS coronovirus1").ti,ab,kw,kf. (502)
12 or/1-11 (2018)
13 exp Anti-Inflammatory Agents, Non-Steroidal/ (0)

14 ((nonsteroid* or non steroid*) adj3 (anti inflammator* or antiinflammator*)).tw. (498)
15 nsaid*.tw. (367)
16 (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. (1216)
17 or/13-16 (1653)
18 12 and 17 (1)

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1 exp coronavirus/ (124)
2 exp Coronavirus Infections/ (139)
3 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw,kf. (8)
4 (coronavirus* or coronovirus* or coronavirinae* or CoV or HCoV*).ti,ab,kw,kf. (88)
5 ("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 "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 Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese* or SARS2 or "SARS-2" or SARScoronavirus2 or "SARS-coronavirus-2" or "SARScoronavirus 2" or "SARS coronavirus2" or SARScoronovirus2 or "SARS-coronovirus-2" or "SARScoronovirus 2" or "SARS coronovirus2").ti,ab,kw,kf. (117)
6 (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*" or pneumonia*) adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (8)
7 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (Wuhan* or Hubei or China* or Chinese* or Huanan*)).ti,ab,kw,kf. (1)
8 Middle East Respiratory Syndrome Coronavirus/ (8)
9 ("middle east respiratory syndrome*" or "middle eastern respiratory syndrome*" or MERSCoV or "MERS-CoV" or MERS).ti,ab,kw,kf. (16)
10 ("severe acute respiratory syndrome*" or SARS).ti,ab,kw,kf. (50)
11 ("SARS-CoV-1" or "SARSCoV-1" or "SARSCoV1" or "SARS-CoV1" or SARSCoV or SARS-CoV or SARS1 or "SARS-1" or SARScoronavirus1 or "SARS-coronavirus-1" or "SARScoronavirus 1" or "SARS coronavirus1" or SARScoronovirus1 or "SARS-coronovirus-1" or "SARScoronovirus 1" or "SARS coronovirus1").ti,ab,kw,kf. (39)
12 or/1-11 (151)
13 exp Anti-Inflammatory Agents, Non-Steroidal/ (137)
14 ((nonsteroid* or non steroid*) adj3 (anti inflammator* or antiinflammator*)).tw. (28)
15 nsaid*.tw. (23)
16 (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. (87)
17 or/13-16 (187)
18 12 and 17 (1)

Appendix C: Evidence selection

A literature search was conducted on 19 March 2020, which identified 156 references (see search strategy for full details). These references were screened using their titles and abstracts and 13 references were obtained in full text 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.

A further literature search was undertaken on 6 April 2020 to identify references published since 19 March 2020. This identified 17 more references, which were screened using their titles and abstracts. None of these were relevant to the research questions.

Excluded studies

Study reference
Cantais, A., Mory, O., Pillet, S. et al. (2014) Epidemiology and microbiological investigations of community-acquired pneumonia in children admitted at the emergency department of a university hospital. Journal of Clinical Virology 60(4): 402-407
Cheng, V.C.C., Lau, S.K.P., Woo, P.C.Y. et al. (2007) Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. Clinical Microbiology Reviews 20(4): 660-694
Cleri, D.J.; Ricketti, A.J.; Vernaleo, J.R. (2010) Severe Acute Respiratory Syndrome (SARS). Infectious Disease Clinics of North America 24(1): 175-202
Day, Michael (2020) COVID-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. BMJ (Clinical research ed.) 368: m1086
Fan, Yunping, Feng, Shaoyan, Xia, Wentong et al. (2012) Aspirin-exacerbated respiratory disease in China: a cohort investigation and literature review. American journal of rhinology & allergy 26(1): e20-2
Greenberg, S.B. (2011) Update on rhinovirus and coronavirus infections. Seminars in Respiratory and Critical Care Medicine 32(4): 433-446
Hui, David S C and Lee, Nelson (2013) Adjunctive therapies and immunomodulating agents for severe influenza. Influenza and other respiratory viruses 7suppl3: 52-9
Kapoor, M., Pringle, K., Kumar, A. et al. (2014) Clinical and laboratory findings of the first imported case of middle east respiratory syndrome coronavirus to the United States. Clinical Infectious Diseases 59(11): 1511-1518
Lin, L., He, D.-P., Han, Y. et al. (2003) Treating severe acute respiratory syndrome with integrated Chinese and Western medicine - A report on 103 hospitalised cases at the Second Affiliated Hospital of Guangzhou University of Chinese Medicine, China. Journal of Chinese Medicine: 5-10
McRitchie, D.; Farooq, W.; Fisher, H.N. (2008) Use of drotrecogin alfa (activated) in a severe acute respiratory syndrome patient with severe sepsis. Canadian Journal of Infectious Diseases and Medical Microbiology 19(3): 258-259

Wong, J.P., Viswanathan, S., Wang, M. et al. (2017) Current and future developments in the treatment of virus-induced hypercytokinemia. Future Medicinal Chemistry 9(2): 169-178
Wong, S.S.Y. and Yuen, K.-Y. (2008) The management of coronavirus infections with particular reference to SARS. Journal of Antimicrobial Chemotherapy 62(3): 437-441
Wong, S.S.Y. and Yuen, K.-Y. (2008) Antiviral therapy for respiratory tract infections. Respirology 13(7): 950-971