

BMJ Open Adverse effects of non-steroidal anti-inflammatory drugs in patients with viral respiratory infections: rapid systematic review

Peter von Philipsborn ^{1,2}, Renke Biallas,^{1,2} Jacob Burns ^{1,2}, Simon Drees,³ Karin Geffert,^{1,2} Ani Movsisyan ^{1,2}, Lisa Maria Pfadenhauer ^{1,2}, Kerstin Sell,^{1,2} Brigitte Strahwald,^{1,2} Jan M Stratil,^{1,2} Eva Rehfues^{1,2}

To cite: von Philipsborn P, Biallas R, Burns J, *et al.* Adverse effects of non-steroidal anti-inflammatory drugs in patients with viral respiratory infections: rapid systematic review. *BMJ Open* 2020;**10**:e040990. doi:10.1136/bmjopen-2020-040990

► Prepublication history and supplemental materials for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2020-040990>).

Received 27 May 2020

Revised 22 September 2020

Accepted 21 October 2020



© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Peter von Philipsborn;
pphilipsborn@ibe.med.uni-muenchen.de

ABSTRACT

Objectives To assess the effects of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with viral respiratory infections on acute severe adverse outcomes, healthcare utilisation, quality of life and long-term survival.

Design Rapid systematic review.

Participants Humans with viral respiratory infections, exposed to systemic NSAIDs.

Primary outcomes Acute severe adverse outcomes, healthcare utilisation, quality of life and long-term survival.

Results We screened 10 999 titles and abstracts and 738 full texts, including 87 studies. No studies addressed COVID-19, Severe Acute Respiratory Syndrome or Middle East Respiratory Syndrome; none examined inpatient healthcare utilisation, quality of life or long-term survival. Effects of NSAIDs on mortality and cardiovascular events in adults with viral respiratory infections are unclear (three observational studies; very low certainty). Children with empyema and gastrointestinal bleeding may be more likely to have taken NSAIDs than children without these conditions (two observational studies; very low certainty). In patients aged 3 years and older with acute respiratory infections, ibuprofen is associated with a higher rate of consultations with general practitioners than paracetamol (one randomised controlled trial (RCT); low certainty). The difference in death from all causes and hospitalisation for renal failure and anaphylaxis between children with fever receiving ibuprofen versus paracetamol is likely to be less than 1 per 10 000 (1 RCT; moderate/high certainty). Twenty-eight studies in adults and 42 studies in children report adverse event counts. Most report that no severe adverse events occurred. Due to methodological limitations of adverse event counts, this evidence should be interpreted with caution.

Conclusions It is unclear whether the use of NSAIDs increases the risk of severe adverse outcomes in patients with viral respiratory infections. This absence of evidence should not be interpreted as evidence for the absence of such risk. This is a rapid review with a number of limitations.

PROSPERO registration number CRD42020176056.

Strengths and limitations of this study

- We conducted a rapid systematic review following Cochrane rapid review guidance and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline.
- We systematically searched three databases and conducted forward-citation and backward-citation searches.
- We followed a prespecified protocol, and clearly state where we deviated from it.
- This is a rapid review, and we applied less quality controls than in the reviews we normally conduct.
- The review is limited to studies in patients with viral respiratory infections and conditions commonly caused by respiratory viruses; we excluded studies on adverse effects of non-steroidal anti-inflammatory drugs in patients with bacterial respiratory infections, which have been summarised in existing reviews.

BACKGROUND

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs, and have a wide range of uses, including treatment of acute and chronic pain, fever and inflammation. NSAIDs include unselective cyclo-oxygenase (COX) inhibitors (eg, ibuprofen, aspirin, diclofenac and naproxen) as well as selective COX 2 inhibitors or cyclo-oxygenase-2 inhibitors (eg, celecoxib, rofecoxib and etoricoxib). NSAIDs are associated with a number of adverse effects, in particular when used at higher doses, over longer periods of time, in the elderly and in patients with relevant comorbidities.^{1–3} Well-established adverse effects include gastrointestinal ulcers and bleeding¹ and renal damage,⁴ as well as elevated cardiovascular risks for some NSAIDs.^{1 5} These potential harms must be balanced with the potential therapeutic benefits of NSAIDs.

Acute viral respiratory infections, in particular influenza, are associated with an elevated risk for a number of severe adverse outcomes, in particular in the elderly and in patients with relevant comorbidities. This includes myocardial infarction,⁶ ischaemic and haemorrhagic stroke,⁷⁻⁹ as well as deep vein thrombosis and pulmonary embolism.¹⁰ Preventing influenza through vaccination is therefore an effective way to reduce cardiovascular events and mortality.¹¹ Acute viral respiratory infections can also trigger a worsening of underlying chronic conditions, including chronic obstructive pulmonary disease¹² and heart failure.^{13 14}

Recently, concerns have been raised that in patients with COVID-19 and other viral respiratory infections, the use of NSAIDs may be associated with an additionally increased risk for severe adverse outcomes, above and beyond the known risks of NSAIDs alone and of acute viral respiratory infections alone.¹⁵⁻¹⁷ In particular, the question has been raised whether the combined exposure to NSAIDs and acute viral respiratory infections (COVID-19 in particular) leads to: (1) specific adverse events that likely would not occur due to either exposure alone; (2) a worsening of the course of the infection or (3) an increase in the rate and severity of the known side effects of NSAIDs.

These concerns, notably regarding COVID-19, led the WHO to request the present rapid review. Specifically, the review aims to assess the effects of systemic NSAIDs in patients with viral respiratory infections on acute severe adverse events (including mortality, acute respiratory distress syndrome, acute organ failure and opportunistic infections), acute healthcare utilisation (including hospitalisation, intensive care unit admission, supplemental oxygen therapy and mechanical ventilation), as well as explicit quality of life measures and long-term survival.

METHODS

Protocol registration

The review was registered with PROSPERO and the Open Science Framework (osf.io/snnp4). Methods are based on Cochrane Rapid Review guidance.¹⁸ Reporting follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

Search strategy and selection criteria

We searched MEDLINE, EMBASE and the WHO COVID-19 database¹⁹ up to 31 March 2020. We conducted forward-citation and backward-citation searches in Scopus using references of existing reviews and included studies. Our full search strategy is shown in the online supplemental appendix.

After removal of duplicate studies, titles and abstracts of all identified records were screened by one review author to select records meeting our inclusion criteria. Subsequently, full texts were screened by one review author. Twenty per cent of all titles and abstracts, and 50% of all full texts were screened by a second review author. We

used Rayyan, a web-based application for title and abstract screening.²⁰ During full-text screening, we documented the reasons for exclusion.

We included studies conducted in humans of any age with viral respiratory infections or conditions commonly caused by respiratory viruses and exposed to systemic NSAIDs of any kind, reporting on acute severe adverse events, acute healthcare utilisation, explicit quality of life measures or long-term survival. We included studies reporting primary empirical data on at least 10 participants, except for studies on COVID-19, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), where studies of any size were eligible. [Tables 1 and 2](#) provide detailed inclusion and exclusion criteria.

We included studies in which at least 50% of all patients in one of the study groups (intervention or control group for randomised controlled trials (RCTs), and cases or controls for case-control studies) met our inclusion criteria (ie, were adults, had a relevant infection or condition, and were exposed to NSAIDs).

We excluded studies in which patients received antibiotics as part of the intervention, taking antibiotic treatment as a proxy for bacterial infection. We did, however, include studies in which varying numbers of participants received antibiotics independent of the intervention over the course of the study.²¹ We also included one study in patients with confirmed influenza infection who received an antibiotic as part of their initial treatment regime.²²

Data analysis

One review author extracted data and assessed risk of bias of included studies using a pretested data extraction form (see online supplemental appendix). We used the Tool to Assess Risk of Bias in Case-Control Studies developed by the Clarity Group at McMaster University for case-control and case-crossover studies,²³ and the Cochrane risk of bias tool adapted by the Cochrane Effective Practice and Organisation of Care group for all remaining study designs.²⁴ We applied Grading of Recommendations Assessment, Development and Evaluation (GRADE) to assess the certainty of evidence, rating evidence as high, moderate, low or very low certainty.²⁵

Due to time constraints and the large number of studies identified, we decided post hoc to restrict full evidence synthesis to studies in adults, as well as to studies in children using study designs most capable of detecting rare severe adverse events (ie, case-control studies and large RCTs with >1000 participants) as these studies best addressed the commissioned review question. For the remaining studies in children, we mapped the evidence, that is, we extracted and tabulated data on key study characteristics and adverse outcomes, but did not assess risk of bias and certainty of evidence.

We had originally planned to extract data on two sets of secondary outcomes (laboratory measures and imaging findings), but decided that this was not feasible within

Table 1 Inclusion criteria

Population	Humans of any age with acute viral respiratory infections , with or without comorbidities (eg, cardiovascular disease, diabetes mellitus, COPD, asthma)	Patients with COVID-19/SARS-CoV-2 Patients with SARS/MERS Patients with other coronavirus infections Patients with other acute viral respiratory infections, including influenza, parainfluenza and rhinovirus infections Patients with conditions commonly caused by respiratory viruses, including children with fever and patients of any age with upper respiratory tract infections, including the common cold, pharyngitis, laryngitis, sore throat and tonsillitis, unless specified as being of bacterial aetiology or treated with antibiotics
Intervention/exposure	Non-steroidal anti-inflammatory drug (NSAID) intake prior or during the acute infection , including oral, intravenous and intramuscular NSAIDs and NSAIDs as suppositories taken or administered for any reason (including treatment of underlying conditions, and treatment of fever, pain and other acute symptoms)	Unselective COX inhibitors: ibuprofen, aspirin (acetylsalicylate), diclofenac, naproxen, indomethacin, ketoprofen, etc Selective COX 2 inhibitors: celecoxib, rofecoxib, etoricoxib, lumiracoxib, valedocoxib, etc
Comparison	No or different NSAID	No NSAID (including other antipyretic and analgesic drugs, for example, paracetamol/acetaminophen) Different dose or application of NSAID Different NSAID (eg, aspirin vs ibuprofen)
Outcomes	Acute severe adverse events, acute healthcare utilisation and longer-term effects	Acute severe adverse events: <ul style="list-style-type: none"> ▶ Mortality ▶ Acute respiratory distress syndrome ▶ Acute organ failure (including acute renal failure) ▶ Cardiovascular events ▶ Opportunistic infections ▶ Severe acute allergic and hypersensitivity reactions ▶ Other, as reported Acute healthcare utilisation: <ul style="list-style-type: none"> ▶ Rate and length of hospitalisation ▶ Rate and length of intensive care unit utilisation ▶ Rate and length of supplemental oxygen therapy ▶ Rate, length and type of mechanical ventilation (invasive vs non-invasive) ▶ Other, as reported Longer-term effects: <ul style="list-style-type: none"> ▶ Explicit quality of life measures ▶ Long-term survival
Study designs	Any systematic empirical study design	Randomised controlled trials Cohort studies Case-control studies Case series with >10 patients Case series with <10 patients (only for COVID-19, SARS and MERS)

COPD, chronic obstructive pulmonary disease; COX, cyclo-oxygenase; MERS, Middle East Respiratory Syndrome; SARS, Severe Acute Respiratory Syndrome.

the timeframe of the review. We had intended to undertake meta-analyses and present forest plots of sufficiently similar studies. This was not feasible in view of substantial heterogeneity in the interventions and outcomes assessed. We therefore summarised findings narratively and through tables.

We extracted and report all measures of treatment effect for the primary outcomes prespecified in our protocol. For dichotomous outcomes this includes risk ratios (RRs) and ORs. We extracted and report adjusted results as provided by the included studies. We included 95% CIs when these were reported by primary studies.

**Table 2** Exclusion criteria

Population	<ul style="list-style-type: none"> ▶ Patients with acute bacterial respiratory infections ▶ Patients with non-respiratory viral infections ▶ Patients with haemorrhagic fevers (including dengue and ebola) ▶ Patients with infections treated with antibiotics ▶ Patients with pneumonia, unless specified explicitly as being of viral aetiology
Intervention / exposure	<ul style="list-style-type: none"> ▶ NSAIDs no longer approved or marketed in key markets (eg, US, Europe) ▶ Non-systemic/topical application of NSAIDs, including lozenges, sprays and microgranules ▶ Corticosteroids ▶ Paracetamol (acetaminophen)
Outcomes	<ul style="list-style-type: none"> ▶ Adverse outcomes of NSAIDs occurring independently of viral respiratory infections, including gastrointestinal effects and renal damage associated with long-term use of any NSAID, and cardiovascular risks due to selective cyclo-oxygenase 2 inhibitors and diclofenac, as these are well established ▶ Allergic and hypersensitivity reactions occurring in general, that is, in the absence of viral respiratory infections ▶ Reye's syndrome and Kawasaki syndrome, as these represent well-studied conditions outside the scope of this review ▶ Implicit quality of life measures (eg, pain, nasal congestion)
Study designs	<ul style="list-style-type: none"> ▶ Non-empirical studies (eg, commentaries) ▶ Animal studies ▶ Mechanistic data

NSAIDs, non-steroidal anti-inflammatory drugs.

Availability of data and materials

The data supporting the conclusions of this article are included within the article and its additional file.

Role of the funding source

This review was funded through staff positions and university funds at the Ludwig-Maximilians-Universität (LMU) Munich, Germany. The review question was set by the WHO, who requested this review from the Chair of Public Health and Health Services Research at the LMU Munich in its capacity as a WHO Collaborating Centre for Evidence-Based Public Health. The authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the WHO.

Patient and public involvement

Patients and the public were not involved in this study.

RESULTS

Results of the search

The PRISMA flow chart is shown in [figure 1](#), and the search log is shown in the online supplemental appendix.

Through database and forward-citation and backward-citation searches we identified 10 999 unique records. Of these, we excluded 10 196 at title and abstract screening stage, leaving 803 studies to be assessed as full texts. We were able to locate and assess the full texts for 738 studies. Overall, 87 studies met the eligibility criteria and were included in our review.

We included 72 RCTs, 7 cohort studies, 3 case–cross-over studies, 3 non-RCTs (NRCTs), 1 case–control study and 1 case series. The total number of participants was 172 381 (median: 174, range: 20–83 915). The median follow-up was 3 days (range: 1 hour to 11 months). We did not identify any study on COVID-19, SARS or MERS meeting the eligibility criteria. All studies related to other acute viral infections, or to conditions, such as upper respiratory tract infections, that are commonly caused by respiratory viruses.

We included 39 studies in our evidence synthesis and 48 studies in our evidence mapping. Studies included in the evidence synthesis comprised 28 RCTs, 3 cohort studies^{26–28} and 2 case–crossover studies^{8 9} in adults, and 3 case–control studies^{29 30} and 4 studies reporting on 1 RCT in children.^{31–34} One retrospective cohort study²⁷ and one RCT²¹ included both adults and children. The latter included participants aged 3 years and older, and did not report results separately for adults and children. With the majority being adults, we included this study in the evidence synthesis for adults. We assessed most of the studies to be at high or unclear risk of bias in at least one domain. Risk of bias of case–control and case–crossover studies is shown in [figure 2](#), and risk of bias of all other study designs in [figure 3](#). Studies included in evidence mapping comprised 39 RCTs, 4 cohort studies, 4 NRCTs and 1 case series in children. Details on the population, intervention and comparison, outcomes and study designs of included studies are provided in the online supplemental appendix.

Findings for adults

Summary of findings for the effects of NSAIDs on mortality and cardiovascular events in adults with viral respiratory infections is shown in [table 3](#). Effects on the rate of consultations with general practitioners are shown in [table 4](#).

One retrospective registry-based cohort study in 683 adults with a follow-up of 60 days reports effects on mortality.²⁷ Results indicate that the effects of NSAIDs on mortality in critically ill adults with influenza during the 2009/2010 H1N1 influenza pandemic are unclear (adjusted RR (aRR): 0.9, 95% CI: 0.5 to 1.6). The CI for this effect estimate is large and includes the possibility of a negative, null or positive effect. This evidence was graded as very low certainty. The same conclusion (very low certainty evidence) is suggested for a subgroup analysis for aspirin only (data shown in online supplemental appendix table 1).

Two case–crossover studies in 9793 patients with myocardial infarction and 29 518 patients with ischaemic or haemorrhagic stroke assessed effects on cardiovascular

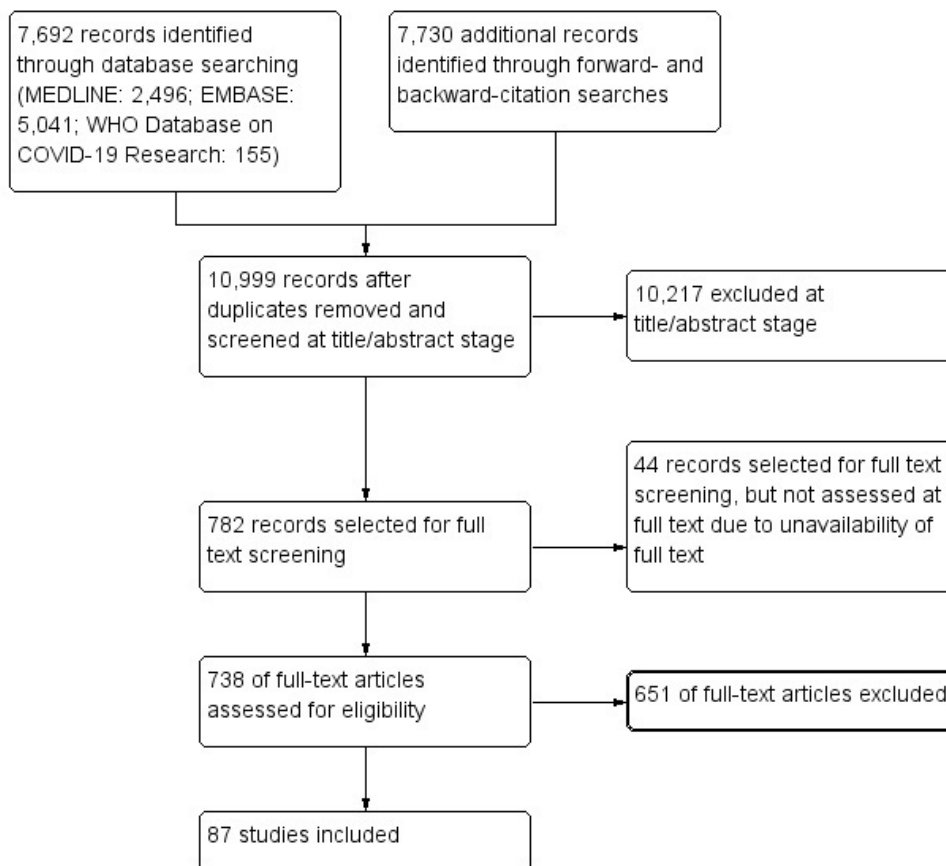


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.

events.^{8 9} Both studies report multiple indirect comparisons, comparing adults without acute respiratory infection and not exposed to NSAIDs to: (1) adults exposed to both an acute respiratory infections and NSAIDs; (2) adults with an acute respiratory infection but not exposed to NSAIDs and (3) adults without an acute respiratory infection but exposed to NSAIDs. Both studies report

higher ORs for the combined exposure to NSAIDs and acute respiratory infections than for the exposure to either acute respiratory infections or NSAIDs alone (see table 4). As the CIs of these ORs overlap we assessed the effect of NSAIDs on cardiovascular events in adults with acute respiratory infections as unclear (very low certainty evidence). Both studies report subgroup analyses based

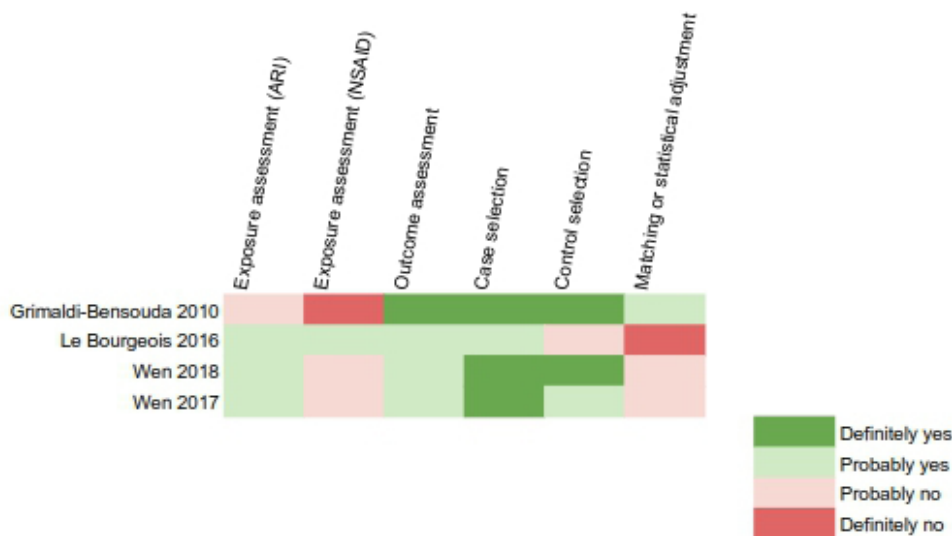


Figure 2 Risk of bias of case-control and case-crossover studies. ARI, acute respiratory infection; NSAID, non-steroidal anti-inflammatory drug.



Figure 3 Risk of bias of studies other than case-control and case-crossover studies.

on dosage and type of application as well as type of NSAID. The subgroup analyses for specific NSAIDs suggest that the differences in the ORs presented in table 4 may be driven by a subset of NSAIDs with a known elevated cardiovascular risk profile (COX-2 inhibitors, diclofenac and mefenamic acid). However, CIs overlap and include the possibility of negative, null or positive effects (very low certainty evidence) (see online supplemental appendix table 1).

We identified 28 RCTs^{21 22 35–60} and 2 cohort studies^{26 28} reporting counts of adverse events. Most of these studies were of short duration (follow-up: 2 hours to 30 days, median: 4.5 days). Most studies were small (median number of participants: 209, range: 30–2341). Sixteen studies report that no or no severe adverse effects were observed.^{22 35 37 39 41 42 44 47–49 52–56 59} Three studies report that adverse effects, classified as severe or serious by the

study authors, occurred, including dyspepsia, nausea and urticaria,²⁸ as well as single cases of syncope,⁴³ pneumonia, meningitis and peritonsillar abscess.²¹ Eleven studies report mild or moderate adverse events, but do not mention severe adverse events.^{26 36 38 40 45 46 50 51 57 58 60}

The most commonly reported mild or moderate adverse events were abdominal pain,^{26 38 40 46 50 51 58} drowsiness or lightheadedness,^{36 40 45 50 57} and nausea.^{26 40 60} Due to the inherent methodological limitations of adverse event counts,⁶¹ and the small sample size and short follow-up of most of these studies, this evidence was not assessed with GRADE, and should be interpreted with caution. One study reporting effects on adverse event counts also reports effects on the rate of consultations, presented below.²¹

One RCT in 889 patients aged 3 years or older with a follow-up of 4 weeks assessed effects on the rate of

Table 3 Use of NSAIDs compared with no use of NSAIDs in adults with acute respiratory infections (ARIs)

Patient or population: adults with ARIs			
Intervention: use of NSAIDs			
Comparison: no use of NSAIDs			
Outcomes	Impact	No of participants (studies)	Certainty of evidence (GRADE)*
Mortality H1N1 influenza Follow-up: 60 days following intensive care unit admission or until death or hospital discharge	Epperly 2016 Risk associated with NSAID use: aRR=0.9 (95% CI: 0.5 to 1.6)	683 (1 retrospective, registry-based cohort study)	⊕○○○ Very low†
Ischaemic stroke Acute respiratory infection Follow-up: exposure in case period (7 days prior to event) was compared with control period (365 days prior to case period)	Wen 2018 Compared with no use of NSAIDs in adults without ARI (baseline): Risk associated with NSAID use and ARI episode: aOR=2.27 (95% CI: 2.00 to 2.58) Risk associated with ARI episode: aOR=2.11 (95% CI: 1.91 to 2.34) Risk associated with NSAID use: aOR=1.38 (95% CI: 1.30 to 1.46)	23 618 (1 case–crossover study)	⊕○○○ Very low†
Haemorrhagic stroke Acute respiratory infection Follow-up: exposure in case period (7 days prior to event) was compared with control period (365 days prior to case period)	Wen 2018 Compared with no use of NSAIDs in adults without ARI (baseline): Risk associated with NSAID use and ARI episode: aOR=2.28 (95% CI: 1.71 to 3.02) Risk associated with ARI episode: aOR=1.63 (95% CI: 1.31 to 2.03) Risk associated with NSAID use: aOR=1.49 (95% CI: 1.31 to 1.69)	5900 (1 case–crossover study)	⊕○○○ Very low†
Myocardial infarction Acute respiratory infection Follow-up: exposure in case period (7 days prior to event) was compared with control period (365 days prior to case period)	Wen 2017 Compared with no use of NSAIDs in adults without ARI (baseline): Risk associated with NSAID use and ARI episode: aOR=3.41 (95% CI: 2.80 to 4.16) Risk associated with ARI episode: aOR=2.65 (95% CI: 2.29 to 3.06) Risk associated with NSAID use: aOR=1.47 (95% CI: 1.33 to 1.62)	9793 (1 case–crossover study)	⊕○○○ Very low†

GRADE Working Group grades of evidence: high certainty—we are very confident that the true effect lies close to that of the estimate of the effect; **moderate certainty**—we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; **low certainty**—our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; **very low certainty**—we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

*All studies included for this comparison were non-randomised; thus each body of evidence started the GRADE assessment as low certainty.

†Downgraded by 1 level for imprecision.

aOR, adjusted OR; aRR, adjusted risk ratio; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NSAIDs, non-steroidal anti-inflammatory drugs.

reconsultations with general practitioners.²¹ Data on 595 patients were included in the analyses. Results indicate that in patients with acute respiratory infections ibuprofen is associated with a higher rate of reconsultations for new or unresolved symptoms or complications than paracetamol (acetaminophen) (OR 1.7, 95% CI: 1.1 to 2.4). The study reports that ‘(m)ost of the 17 ‘complications’ recorded were not serious’.²¹ This evidence was considered to be of low certainty due to study limitations and indirectness of evidence.

Findings for children

Summary of findings for effects of NSAIDs on mortality and risk for empyema, gastrointestinal bleeding, death from all causes and hospitalisation in children is shown in online supplemental appendix tables 2 and 3.

One cohort study in 838 children (mean age: 7 years) with a follow-up of 60 days reports effects on mortality.²⁷ Results indicate that the effects of NSAIDs on mortality in critically ill children with H1N1 influenza are unclear (aRR 1.5, 95% CI: 0.7 to 3.2; very low certainty evidence).

One matched case–control study in 166 children aged 3–15 years with acute viral infections reports effects on risk for empyema (follow-up: 15 days).³⁰ One case–crossover study in 177 children (aged 2 months to 16 years) with fever reports effects on gastrointestinal bleeding (follow-up: 7 days).²⁹ Results indicate that children with empyema and gastrointestinal bleeding may be more likely to have been exposed to NSAIDs than children without these conditions (adjusted OR (aOR) for empyema: 2.8, 95% CI: 1.4 to 5.6; aOR for gastrointestinal bleeding: 8.2, 95% CI: 2.6 to 26.0; very low certainty evidence).^{29 30}

Four studies on one RCT including 83 915 children report effects on death from all causes and risk for hospitalisation (follow-up: 4 weeks), comparing ibuprofen with acetaminophen (paracetamol).^{31–34} The study had 80% power to detect a 0.2% difference in hospitalisation for any cause, and differences of 1 per 10 000 for hospitalisation for acute gastrointestinal bleeding, acute renal failure and anaphylaxis. Our

Table 4 Use of ibuprofen versus paracetamol in participants aged ≥ 3 years with acute respiratory tract infections

Patient or population: participants aged ≥ 3 years with acute respiratory tract infections

Intervention: use of ibuprofen

Comparison: use of paracetamol

Outcomes	Impact	No of participants (studies)	Certainty of the evidence (GRADE)
Reconsultation with general practitioner (with new or unresolved symptoms or complications within 1 month)	Little 2013 Risk associated with use of ibuprofen: aRR 1.67 (95% CI: 1.12 to 2.38)	595 participants (1 RCT)	$\oplus\oplus\circ\circ$ Low*†

GRADE Working Group grades of evidence: high certainty—we are very confident that the true effect lies close to that of the estimate of the effect; **moderate certainty**—we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; **low certainty**—our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; **very low certainty**—we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

*Downgraded evidence by 1 level for study limitations: lack of blinding.

†Downgraded evidence by 1 level for indirectness: advice to use versus direct use.

aRR, adjusted risk ratio; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomised controlled trial.

assessment of the certainty of evidence for differences between the ibuprofen and the acetaminophen group is based on these thresholds for relevant differences. Results indicate that the difference in the rate of death from all causes and of hospitalisation for acute renal failure and anaphylaxis is likely to be smaller than 1 per 10 000, that the difference in hospitalisation for acute gastrointestinal bleeding is likely to be smaller than 2 per 10 000, and the difference in hospitalisation for any cause less than 20 per 10 000 (moderate to high certainty evidence).

Forty-two RCTs, five cohort studies and one case series in children report adverse event counts. Most studies report some mild or moderate adverse effects but do not mention severe adverse effects (24 studies). Ten studies explicitly report that there had been no severe adverse effects during the follow-up period. In six studies, severe adverse effects were observed. The remaining eight studies state that there had been no adverse effects but do not specify their severity. Due to the inherent methodological limitations of adverse event counts, and the small sample size and short

follow-up of most of these studies, this evidence should be interpreted with caution.

DISCUSSION

We identified 33 studies in adults examining adverse outcomes of NSAIDs in patients with viral respiratory infections or conditions commonly caused by respiratory viruses. None of these studies was in patients with COVID-19, SARS or MERS. Therefore, all evidence included in this review should be considered as indirect evidence for the use of NSAIDs in patients with COVID-19. Potential adverse effects of NSAIDs specific to COVID-19, SARS or MERS could therefore not be explored in our review.^{15 62} Evidence obtained for adults was of very low to low certainty, and should be interpreted with caution. We did not find conclusive evidence for relevant effects of NSAIDs on mortality or other severe acute adverse outcomes in adults with viral respiratory infections. Low certainty evidence from one RCT indicates that in participants aged 3 years and older with respiratory infections ibuprofen compared with acetaminophen (paracetamol) is associated with a higher rate of reconsultations with general practitioners.²¹

We identified 56 eligible studies in children. Most of these were small and of short duration, and provide only limited evidence on severe adverse effects. One large RCT in children provides moderate to high certainty evidence that the difference in the rate of death from all causes and of hospitalisation for acute renal failure and anaphylaxis is likely to be smaller than 1 per 10 000, that the difference in hospitalisation for acute gastrointestinal bleeding is likely to be smaller than 2 per 10 000, and the difference in hospitalisation for any cause less than 20 per 10 000.³¹⁻³⁴

We did not identify any studies reporting on measures of inpatient healthcare utilisation, long-term survival or explicit quality of life measures.

This is a rapid review, conducted over 2 weeks, with a number of limitations:

- ▶ Searches were limited to three databases, that is, MEDLINE, EMBASE and the WHO COVID-19 database, complemented with forward-citation and backward-citation searches. We did not search for or include sources of grey literature or preprints, and considered only studies published in English or German.
- ▶ Screening criteria and guidance were refined and calibrated while screening was underway, and only 20% of titles and abstracts and 50% of full texts were screened in duplicate.
- ▶ Data extraction and risk of bias assessment were done by one review author only. To account for potential errors, all data presented in tables or figures as part of the evidence synthesis were checked for their correctness by a second review author.
- ▶ Risk of bias assessment and full evidence synthesis was limited to studies in adults and to those studies in

children most capable of detecting rare severe adverse events (ie, case–control studies and large RCTs). The decision to exclude other studies in children from evidence synthesis was taken post hoc.

- ▶ All steps of the review process were undertaken rapidly, with fewer quality control measures than during the systematic reviews we usually conduct.
- ▶ We were unable to undertake all the subgroup analyses foreseen in our protocol: many were not feasible due to too much heterogeneity between studies, for others (eg, subgroup analyses by age or sex) we lacked the time.

The evidence identified in this review is also characterised by a number of limitations:

- ▶ We included not only studies in patients with confirmed viral respiratory infections, but also studies in patients with conditions commonly caused by respiratory viruses, such as upper respiratory tract infections and fever in children. It is likely that not all participants of these studies had viral respiratory infections.
- ▶ We did not consider studies on patients with bacterial infections; these can occur as a super-infection in patients with viral respiratory infections. Potential adverse effects of NSAIDs in patients with bacterial infections and conditions commonly caused by bacterial infections, including community-acquired pneumonia, have been summarised in existing reviews⁶³ and were beyond the scope of this rapid review.
- ▶ NSAIDs constitute a diverse group of drugs with diverging risk profiles for different populations and conditions. Not all studies distinguished between different types of NSAIDs. Some of the older studies are likely to have included patients taking NSAIDs that are no longer available on the market due to their known side effects.
- ▶ Some studies provided only indirect comparisons, which can be informative, but do not provide effect estimates for the actual comparison of interest, that is, NSAID use versus no NSAID use among individuals with a viral respiratory infection.^{8 9}
- ▶ We identified only one RCT that included a sufficiently large number of participants to identify rare severe adverse events.^{31–34} The remaining evidence derives from smaller RCTs, which are underpowered for detecting rare severe adverse events, and from case–control and cohort studies with methodological limitations.

Conclusions

We did not find conclusive evidence showing that NSAIDs in patients with viral respiratory infections are associated with additional risks for severe acute adverse outcomes, above and beyond the known risks associated with NSAIDs alone and viral respiratory infections alone. This absence of evidence should not be interpreted as evidence for the absence of such risks. Most of the evidence was of very low to low certainty, and should be interpreted with caution.

To improve the evidence base, future studies should use robust study design, sufficiently large sample sizes and follow-up periods, and follow relevant reporting guidelines. When using NSAIDs, existing guidance should be considered, including approved product information for specific NSAIDs and relevant clinical guidelines.

Author affiliations

¹Chair of Public Health and Health Services Research in its capacity as a WHO Collaborating Centre for Evidence-Based Public Health, Institute for Medical Information Processing, Biometry and Epidemiology (IBE), Ludwig Maximilians University Munich Medical Faculty, Munchen, Germany

²Pettenkofer School of Public Health, Munich, Germany

³Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

Twitter Simon Drees @simon_drees and Brigitte Strahwald @strahwald

Acknowledgements The authors of this review would like to thank Irma Klerings for advice on the search strategy, Gerald Gartlehner for advice on protocol development, and Katharina Wabnitz and Torben Sell for support in obtaining full texts of studies included in this review. We are also grateful to Susan L Norris and the various clinical experts currently working on COVID-19 at the WHO that defined the review question and offered guidance despite the enormous pressures on everyone's time.

Contributors PvP and ER developed the protocol with input from all review authors, and PvP coordinated the overall review process. PvP took the lead in putting together the report, supported by ER and all review authors. All other review authors are listed in alphabetical order, with every single one having made significant contributions, both intellectually and in terms of time commitment. JMS and PvP developed the search strategy and conducted the searches. AM, BS, JB, JMS, KG, KS, LMP, PvP, RB and SD screened studies for eligibility, extracted data and assessed risk of bias. AM, ER, JB, JMS and PvP conducted the GRADE assessment. All review authors contributed to the narrative and tabular evidence synthesis and manuscript preparation.

Funding Funded through staff positions and other funds of the Ludwig-Maximilians-Universität München (LMU Munich).

Disclaimer This systematic review was requested by the WHO. The authors alone are responsible for the views expressed in this systematic review and they do not necessarily represent the decisions, policy or views of the WHO.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information. The data supporting the conclusions of this article are included within the article and its additional file.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Peter von Philipsborn <http://orcid.org/0000-0001-7059-6944>

Jacob Burns <http://orcid.org/0000-0003-4015-6862>

Ani Movsisyan <http://orcid.org/0000-0003-0258-8912>

Lisa Maria Pfadenhauer <http://orcid.org/0000-0001-5038-8072>

REFERENCES

- 1 Coxib and traditional NSAID Trialists' (CNT) Collaboration, Bhala N, Emberson J, *et al.* Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013;382:769–79.
- 2 McGettigan P, Platona A, Henry DA. Renal and cardiovascular toxicity of non-steroidal anti-inflammatory drugs. *Inflammopharmacology* 2000;8:1–18.
- 3 Kearney PM, Baigent C, Godwin J, *et al.* Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006;332:1302–8.
- 4 Ungprasert P, Cheungpasitporn W, Crowson CS, *et al.* Individual non-steroidal anti-inflammatory drugs and risk of acute kidney injury: a systematic review and meta-analysis of observational studies. *Eur J Intern Med* 2015;26:285–91.
- 5 Trelle S, Reichenbach S, Wandel S, *et al.* Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011;342:c7086.
- 6 Barnes M, Heywood AE, Mahimbo A, *et al.* Acute myocardial infarction and influenza: a meta-analysis of case-control studies. *Heart* 2015;101:1738–47.
- 7 Warren-Gash C, Smeeth L, Hayward AC. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review. *Lancet Infect Dis* 2009;9:601–10.
- 8 Wen Y-C, Hsiao F-Y, Chan KA, *et al.* Acute respiratory infection and use of nonsteroidal anti-inflammatory drugs on risk of acute myocardial infarction: a nationwide case-crossover study. *J Infect Dis* 2017;215:503–9.
- 9 Wen Y-C, Hsiao F-Y, Lin Z-F, *et al.* Risk of stroke associated with use of nonsteroidal anti-inflammatory drugs during acute respiratory infection episode. *Pharmacoepidemiol Drug Saf* 2018;27:645–51.
- 10 Smeeth L, Cook C, Thomas S, *et al.* Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. *Lancet* 2006;367:1075–9.
- 11 Clar C, Oseni Z, Flowers N, *et al.* Influenza vaccines for preventing cardiovascular disease. *Cochrane Database System Reviews* 2015;5:CD005050.
- 12 Zwaans WAR, Mallia P, van Winden MEC, *et al.* The relevance of respiratory viral infections in the exacerbations of chronic obstructive pulmonary disease—a systematic review. *J Clin Virol* 2014;61:181–8.
- 13 Kadoglou NPE, Bracke F, Simmers T, *et al.* Influenza infection and heart failure—vaccination may change heart failure prognosis? *Heart Fail Rev* 2017;22:329–36.
- 14 Sandoval C, Walter SD, Krueger P, *et al.* Risk of hospitalization during influenza season among a cohort of patients with congestive heart failure. *Epidemiol Infect* 2007;135:574–82.
- 15 Day M. Covid-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. *BMJ* 2020;368:m1086.
- 16 Little P. Non-Steroidal anti-inflammatory drugs and covid-19. *BMJ* 2020;368:m1185.
- 17 Heneghan C, Brassey J. Nsaids in acute respiratory infection, 2020. Available: www.cebm.net/covid-19/nsaids-in-acute-respiratory-infection/ [Accessed 5 Mar 2020].
- 18 Garrity C, Gartlehner G, Kamel C, *et al.* *Cochrane rapid reviews: interim guidance from the Cochrane rapid reviews methods group: cochrane*, 2020.
- 19 WHO. Database of publications on coronavirus disease (COVID-19), 2020. Available: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov> [Accessed 25 Mar 2020].
- 20 Ouzzani M, Hammady H, Fedorowicz Z, *et al.* Rayyan—a web and mobile APP for systematic reviews. *Syst Rev* 2016;5:210.
- 21 Little P, Moore M, Kelly J, *et al.* Ibuprofen, paracetamol, and steam for patients with respiratory tract infections in primary care: pragmatic randomised factorial trial. *BMJ* 2013;347:f6041.
- 22 Hung IFN, To KKW, Chan JFW, *et al.* Efficacy of clarithromycin-naproxen-oseltamivir combination in the treatment of patients hospitalized for influenza A(H3N2) infection: an open-label randomized, controlled, phase IIb/III trial. *Chest* 2017;151:1069–80.
- 23 CLARITY Group. Tool to assess risk of bias in case control studies, 2020. Available: www.evidencepartners.com/wp-content/uploads/2017/09/Tool-to-Assess-Risk-of-Bias-in-Case-Control-Studies.pdf [Accessed 24 Mar 2020].
- 24 EPOC C. Suggested risk of bias criteria for EPOC reviews, 2017. Available: https://epoc.cochrane.org/sites/epoc.cochrane.org/files/public/uploads/Resources-for-authors2017/suggested_risk_of_bias_criteria_for_epoc_reviews.pdf [Accessed 22 Mar 2020].
- 25 Hultcrantz M, Rind D, Akl EA, *et al.* The GRADE working group clarifies the construct of certainty of evidence. *J Clin Epidemiol* 2017;87:4–13.
- 26 Grunthal S, Gessner U. Symptomatic treatment of common colds with combination preparations: a comparative observational study. *Pharmazeutische Zeitung* 2008;153:58–68.
- 27 Epperly H, Vaughn FL, Mosholder AD, *et al.* Nonsteroidal anti-inflammatory drug and aspirin use, and mortality among critically ill pandemic H1N1 influenza patients: an exploratory analysis. *Jpn J Infect Dis* 2016;69:248–51.
- 28 Ottaviani A, Mantovani M, Scaricabarozzi I. A multicentre clinical study of nimesulide in inflammatory diseases of the ear, nose and throat. *Drugs* 1993;46:96–9.
- 29 Grimaldi-Bensouda L, Abenheim L, Michaud L, *et al.* Clinical features and risk factors for upper gastrointestinal bleeding in children: a case-crossover study. *Eur J Clin Pharmacol* 2010;66:831–7.
- 30 Le Bourgeois M, Ferroni A, Leruez-Ville M, *et al.* Nonsteroidal anti-inflammatory drug without antibiotics for acute viral infection increases the empyema risk in children: a matched case-control study. *J Pediatr* 2016;175:47–53.
- 31 Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. *JAMA* 1995;273:929–33.
- 32 Lesko SM, Mitchell AA. Renal function after short-term ibuprofen use in infants and children. *Pediatrics* 1997;100:954–7.
- 33 Lesko SM, Mitchell AA. The safety of acetaminophen and ibuprofen among children younger than two years old. *Pediatrics* 1999;104:e39.
- 34 Lesko SM, Louik C, Vezina RM, *et al.* Asthma morbidity after the short-term use of ibuprofen in children. *Pediatrics* 2002;109:e20.
- 35 Azuma A, Kudoh S, Nakashima M, *et al.* A double-blind study of zaltoprofen for the treatment of upper respiratory tract infection. *Pharmacology* 2010;85:41–7.
- 36 Azuma A, Kudoh S, Nakashima M, *et al.* Antipyretic and analgesic effects of zaltoprofen for the treatment of acute upper respiratory tract infection: verification of a noninferiority hypothesis using loxoprofen sodium. *Pharmacology* 2011;87:204–13.
- 37 Bachert C, Chuchalin AG, Eisebitt R, *et al.* Aspirin compared with acetaminophen in the treatment of fever and other symptoms of upper respiratory tract infection in adults: a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, single-dose, 6-hour dose-ranging study. *Clin Ther* 2005;27:993–1003.
- 38 Bettini R, Grossi E, Rapazzini P, *et al.* Diclofenac sodium versus acetylsalicylic acid: a randomized study in febrile patients. *J Int Med Res* 1986;14:95–100.
- 39 Boureau F, Pelen F, Verriere F, *et al.* Evaluation of ibuprofen vs paracetamol analgesic activity using a sore throat pain model. *Clin Drug Investig* 1999;17:1–8.
- 40 Broggin M, Bott V, Benvenuti C. Flurbiprofen versus ASA in influenza symptomatology: a double-blind study. *Int J Clin Pharmacol Res* 1986;6:485–8.
- 41 Ebel DL, Shih WJ, Rhymer AR. A multi-centre, double-blind randomized study to assess the efficacy and tolerance of sulindac versus placebo in the symptomatic treatment of patients with upper respiratory tract infection. *Curr Med Res Opin* 1985;9:666–75.
- 42 Eccles R, Loose I, Jawad M, *et al.* Effects of acetylsalicylic acid on sore throat pain and other pain symptoms associated with acute upper respiratory tract infection. *Pain Med* 2003;4:118–24.
- 43 Eccles R, Voelker M. Analgesic and decongestant efficacy of the combination of aspirin with pseudoephedrine in patients with symptoms of upper respiratory tract infection. *Clin Pharmacol Drug Dev* 2014;3:118–25.
- 44 Gehanno P, Dreiser RL, Ionescu E, *et al.* Lowest effective single dose of diclofenac for antipyretic and analgesic effects in acute febrile sore throat. *Clin Drug Investig* 2003;23:263–71.
- 45 Goto M, Kawamura T, Shimbo T, *et al.* Influence of loxoprofen use on recovery from naturally acquired upper respiratory tract infections: a randomized controlled trial. *Intern Med* 2007;46:1179–86.
- 46 Graham NM, Burrell CJ, Douglas RM, *et al.* Adverse effects of aspirin, acetaminophen, and ibuprofen on immune function, viral shedding, and clinical status in rhinovirus-infected volunteers. *J Infect Dis* 1990;162:1277–82.
- 47 Grebe W, Ionescu E, Gold MS, *et al.* A multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled, parallel-group comparison of diclofenac-K and ibuprofen for the treatment of adults with influenza-like symptoms. *Clin Ther* 2003;25:444–58.
- 48 Llor C, Moragas A, Bayona C, *et al.* Efficacy of anti-inflammatory or antibiotic treatment in patients with non-complicated acute bronchitis and discoloured sputum: randomised placebo controlled trial. *BMJ* 2013;347:f5762.
- 49 Loose I, Winkel M, Clinical WM. Clinical, double-blind, placebo-controlled study investigating the combination of acetylsalicylic acid and pseudoephedrine for the symptomatic treatment of nasal

- congestion associated with common cold. *Arzneimittelforschung* 2004;54:513–21.
- 50 Milvio C. Nimesulide for the treatment of painful inflammatory process in the ear, nose and throat areas: a double-blind controlled study with benzydamine. *J Int Med Res* 1984;12:327–32.
- 51 Nouri E, Monti T. Nimesulide granules for the treatment of acute inflammation of the ear, nose or throat. *Drugs* 1993;46:103–6.
- 52 Schachtel BP, Fillingim JM, Thoden WR, *et al.* Sore throat pain in the evaluation of mild analgesics. *Clin Pharmacol Ther* 1988;44:704–11.
- 53 Schachtel BP, Fillingim JM, Lane AC, *et al.* Caffeine as an analgesic adjuvant. A double-blind study comparing aspirin with caffeine to aspirin and placebo in patients with sore throat. *Arch Intern Med* 1991;151:733–7.
- 54 Schachtel BP, Pan S, Kohles JD, *et al.* Utility and sensitivity of the sore throat pain model: results of a randomized controlled trial on the COX-2 selective inhibitor valdecoxib. *J Clin Pharmacol* 2007;47:860–70.
- 55 Schachtel BP, McCabe D, Berger M, *et al.* Efficacy of low-dose celecoxib in patients with acute pain. *J Pain* 2011;12:756–63.
- 56 Smith AP, Nutt DJ. Effects of upper respiratory tract illnesses, ibuprofen and caffeine on reaction time and alertness. *Psychopharmacology* 2014;231:1963–74.
- 57 Sperber SJ, Sorrentino JV, Riker DK, *et al.* Evaluation of an alpha agonist alone and in combination with a nonsteroidal antiinflammatory agent in the treatment of experimental rhinovirus colds. *Bull N Y Acad Med* 1989;65:145–60.
- 58 Sperber SJ, Hendley JO, Hayden FG, *et al.* Effects of naproxen on experimental rhinovirus colds. A randomized, double-blind, controlled trial. *Ann Intern Med* 1992;117:37–41.
- 59 Weckx LLM, Ruiz JE, Duperly J, *et al.* Efficacy of celecoxib in treating symptoms of viral pharyngitis: a double-blind, randomized study of celecoxib versus diclofenac. *J Int Med Res* 2002;30:185–94.
- 60 Younkin SW, Betts RF, Roth FK, *et al.* Reduction in fever and symptoms in young adults with influenza A/Brazil/78 H1N1 infection after treatment with aspirin or amantadine. *Antimicrob Agents Chemother* 1983;23:577–82.
- 61 Peryer G, Golder S, Junqueira DR, *et al.* Chapter 19: Adverse effects. In: Higgins J, Thomas J, eds. *Cochrane handbook version 6*. Wiley, 2019.
- 62 Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 2020;8:e21.
- 63 Voiriot G, Philippot Q, Elabbadi A, *et al.* Risks related to the use of non-steroidal anti-inflammatory drugs in community-acquired pneumonia in adult and pediatric patients. *J Clin Med* 2019;8:786