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BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040990
Article Type:	Original research
Date Submitted by the Author:	27-May-2020
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Keywords:	Adverse events < THERAPEUTICS, Respiratory infections < THORACIC MEDICINE, CLINICAL PHARMACOLOGY, VIROLOGY

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

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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 utilization, 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 utilization, 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, SARS or MERS; none examined inpatient healthcare utilization, quality of life or long-term survival. Effects of NSAIDs on mortality and cardiovascular events in adults with viral respiratory infections are unclear (3 observational studies; very low certainty). Children with empyema and gastrointestinal bleeding may be more likely to have taken NSAIDs than children without these conditions (2 observational studies; very low certainty). In patients aged 3 years and older with acute respiratory infections, ibuprofen is associated with a higher rate of re-consultations with general practitioners than paracetamol (1 randomized controlled trial (RCT); low certainty). The difference in death from all causes and hospitalization 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 events 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.

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Registration: Registered with PROSPERO (CRD42020176056) and the Open Science Framework (osf.io/snrp4).

Keywords: non-steroidal anti-inflammatory drugs, viral respiratory infections, adverse effects, side effects, COVID-19

Article Summary

Strengths and limitations of this study:

- We conducted a rapid systematic review following Cochrane rapid review guidance and the PRISMA guideline
- We systematically searched three databases and conducted forward- and backward-citation searches
- We followed a pre-specified 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 NSAIDs in patients with bacterial respiratory infections, which have been summarised in existing reviews

Wordcount: 3,454 words

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

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include unselective cyclooxygenase (COX) inhibitors (e.g. ibuprofen, aspirin, diclofenac and naproxen) as well as selective COX 2 inhibitors or coxibs (e.g. 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 co-morbidities.[1-3] Well-established adverse effects include gastrointestinal ulcers and bleeding[1] 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 co-morbidities. This includes myocardial infarction,[6] ischemic and hemorrhagic 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 disease (COPD)[12] 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: i) specific adverse events that likely would not occur due to either exposure alone; ii) a worsening of the course of the infection; or iii) an increase in the rate and severity of the known side effects of NSAIDs.

These concerns, notably regarding COVID-19, led the World Health Organization (WHO) to request the present rapid review. Specifically, the review aims to assess the effects of systemic NSAIDs in patients

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with viral respiratory infections on acute severe adverse events (including mortality, acute respiratory distress syndrome, acute organ failure and opportunistic infections), acute healthcare utilization (including hospitalization, 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 (registration number: CRD42020176056) and the Open Science Framework (osf.io/snrp4). Methods are based on Cochrane Rapid Review guidance.[18] Reporting follows the PRISMA guideline.

Search strategy and selection criteria

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

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severe adverse events, acute healthcare utilization, 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 (i.e. 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 pre-tested data extraction form (supplementary 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 (EPOC) group for all remaining study designs.[24] We applied GRADE to assess the certainty of evidence, rating evidence as high, moderate, low or very low certainty.[25]

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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 (i.e. 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, i.e. 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 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 pre-specified in our protocol. For dichotomous outcomes this includes risk ratios (RRs) and odds ratios (ORs). We extracted and report adjusted results as provided by the included studies. We included 95% confidence intervals (CIs) when these were reported by primary studies.

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 Munich, Germany. The review question was set by 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

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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 supplementary appendix. Through database and forward- 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, seven cohort studies, three case-crossover studies, three non-randomised controlled trials (NRCTs), one case-control study and one case series. The total number of participants was 172,381 (median: 174, range: 20 to 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, three cohort studies[26-28] and two case-crossover

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studies[8 9] in adults, and three case-control studies [29 30] and four studies reporting on one RCT in children.[31-34] One retrospective cohort study[27] and one RCT[21] included both adults and children. The latter included participants aged three 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, four cohort studies, four NRCTs and one case series in children. Details on the population, intervention and comparison, outcomes and study designs of included studies are provided in the supplementary appendix.

Findings for adults

Summary of findings for the effects of NSAIDs on mortality and cardiovascular events in adults with viral respiratory infections are shown in Table 3. Effects on the rate of re-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 risk ratio (aRR): 0.9, 95% CI: 0.5-1.6). The confidence interval 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 the supplementary appendix).

Two case-crossover studies in 9,793 patients with myocardial infarction and 29,518 patients with ischemic or hemorrhagic stroke assessed effects on cardiovascular events.[8 9] Both studies report

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multiple indirect comparisons, comparing adults without acute respiratory infection and not exposed to NSAIDs to: i) adults exposed to both an acute respiratory infections and NSAIDs; ii) adults with an acute respiratory infection but not exposed to NSAIDs; and iii) adults without an acute respiratory infection but exposed to NSAIDs. Both studies report higher odds ratios (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 confidence intervals 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 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 (coxibs, diclofenac and mefenamic acid). However, confidence intervals overlap, and include the possibility of negative, null or positive effects (very low certainty evidence) (see supplementary appendix).

We identified 28 RCTs[21 22 35-60] and two 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 to 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 syncopation[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 re-consultations, presented below.[21]

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One RCT in 889 patients aged 3 years or older with a follow-up of four weeks assessed effects on the rate of re-consultations 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 re-consulations 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 are shown in Tables s1 and s2 in the supplementary appendix.

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: 0.7-3.2; 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 (aOR for empyema: 2.8, 95% CI: 1.4-5.6; aOR for gastrointestinal bleeding: 8.2, 95% CI: 2.6-26.0; very low certainty evidence).[29 30]

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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 percentage point 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 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)

Fourty-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]

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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 to acetaminophen (paracetamol) is associated with a higher rate of re-consultations 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 two weeks, with a number of limitations:

- Searches were limited to three databases, i.e. MEDLINE, EMBASE and the WHO COVID-19 database, complemented with forward- and backward-citation searches. We did not search for or include sources of grey literature or pre-prints, 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.

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- 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 (i.e. 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 (e.g. 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 reviews[63] 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

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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, i.e. NSAID use vs. 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. The potential harms associated with NSAIDs must be balanced with their potential therapeutic benefits. Existing guidance should be considered, including approved product information for specific NSAIDs and clinical guidelines on respiratory infections.

Captions:

- Figure 1: PRISMA flow chart
- Figure 2: Risk of bias of case-control and case-crossover studies
- Figure 3: Risk of bias of studies other than case-control and case-crossover studies
- Table 1: Inclusion criteria
- Table 2: Exclusion criteria

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- Table 3: Summary of findings for the effects of NSAIDs on mortality and cardiovascular events in adults with viral respiratory infections
- Table 4: Summary of findings for the effects of NSAIDs on the rate of re-consultations with general practitioners in patients with acute respiratory infections

Tables

Table 1

Table 1: Inclusion criteria		
Population	**Humans of any age with acute viral respiratory infections**, with or without co-morbidities (e.g. 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 etiology 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 and ketoprofen, etc.
		Selective COX 2 inhibitors: Celecoxib, Rofecoxib, Etoricoxib, Lumiracoxib, and Valecoxib, etc.
Comparison	**No or different NSAID**	No NSAID (including other antipyretic and analgesic drugs, e.g. paracetamol/ acetaminophen)
		Different dose or application of NSAID
		Different NSAID (e.g. aspirin versus ibuprofen)
Outcomes	**Acute severe adverse events, acute healthcare utilization and longer-term effects**	**Acute severe adverse events:** ● Mortality ● Acute respiratory distress syndrome (ARDS) ● Acute organ failure (including acute renal failure) ● Cardiovascular events ● Opportunistic infections ● Severe acute allergic and hypersensitivity reactions ● Other, as reported
		Acute healthcare utilization:

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		• Rate and length of hospitalization • Rate and length of intensive care unit (ICU) utilization • Rate and length of supplemental oxygen therapy • Rate, length and type of mechanical ventilation (invasive vs. non-invasive) • Other, as reported
		Longer-term effects: • Explicit quality of life measures • Long-term survival
Study designs	**Any systematic empirical study design**	Randomized controlled trials
		Cohort studies
		Case-control-studies
		Case series with > 10 patients
		Case series with < 10 patients (only for COVID-19, SARS and MERS)

Table 2

Table 2: Exclusion criteria	
Population	• Patients with acute bacterial respiratory infections • Patients with non-respiratory viral infections • Patients with hemorrhagic fevers (including Dengue and Ebola) • Patients with infections treated with antibiotics • Patients with pneumonia, unless specified explicitly as being of viral etiology
Intervention / Exposure	• NSAIDs no longer approved or marketed in key markets (e.g. US, Europe) • Non-systemic/topical application of NSAIDs, including lozenges, sprays, and microgranules • Corticosteroids • Paracetamol (acetaminophen)
Outcomes	• 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 cyclooxygenase (COX) 2 inhibitors and diclofenac, as these are well established • Allergic and hypersensitivity reactions occurring in general, i.e. 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 (e.g. pain, nasal congestion)
Study designs	• Non-empirical studies (e.g. commentaries) • Animal studies • Mechanistic data

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Table 3

Table 3. Use of NSAIDs compared to no use of NSAIDs in adults with acute respiratory infections

Patient or population: adults with acute respiratory infections (ARI)
Intervention: use of NSAIDs
Comparison: no use of NSAIDs

Outcomes	Impact	№ of participants (studies)	Certainty of the 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 - 1.6)	683 (1 retrospective, registry-based cohort study)	⊕◯◯◯ VERY LOW [a]
Ischemic stroke Acute respiratory infection Follow-up: exposure in case period (7 days prior to event) was compared to control period (365 days prior to case period)	**Wen 2018** Compared to no use of NSAIDs in adults without ARI (baseline): Risk associated with NSAID use and ARI episode: aOR = 2.27 (95% CI: 2.00- 2.58) Risk associated with ARI episode: aOR = 2.11 (95% CI: 1.91 - 2.34) Risk associated with NSAID use: aOR = 1.38 (95% CI: 1.30 - 1.46)	23618 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
Hemorrhagic stroke Acute respiratory infection Follow-up: exposure in case period (7 days prior to event) was compared to control period (365 days prior to case period)	**Wen 2018** Compared to no use of NSAIDs in adults without ARI (baseline): Risk associated with NSAID use and ARI episode: aOR = 2.28 (95% CI: 1.71-3.02) Risk associated with ARI episode: aOR = 1.63 (95% CI: 1.31-2.03) Risk associated with NSAID use: aOR = 1.49 (95% CI: 1.31-1.69)	(5900 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
Myocardial infarction Acute respiratory infection Follow-up: exposure in case period (7 days prior to event) was compared to control period (365 days prior to case period)	**Wen 2017** Compared to no use of NSAIDs in adults without ARI (baseline): Risk associated with NSAID use and ARI episode: aOR = 3.41 (95% CI: 2.80-4v16) Risk associated with ARI episode: aOR = 2.65 (95% CI: 2.29-3.06) Risk associated with NSAID use: aOR = 1.47 (95% CI: 1.33-1.62)	9793 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]

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

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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

Explanations: a. Downgraded by 1 level for imprecision.

Table 4

Table 4: Use of ibuprofen vs. 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	№ of participants (studies)	Certainty of the evidence (GRADE)
Re-consultation 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: 1.12-2.38)	595 participants (1 RCT)	⨁⨁◯◯ LOW [a,b]

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

Explanations
a. Downgraded evidence by 1 level for study limitations: lack of blinding
b. Downgraded evidence by 1 level for indirectness: advice to use vs. direct use.

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Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

Funding

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

Author Contributions

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.

Disclaimer

This systematic review was requested by the World Health Organization. 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 World Health Organization.

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

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various clinical experts currently working on COVID-19 at WHO that defined the review question and offered guidance despite the enormous pressures on everyone's time.

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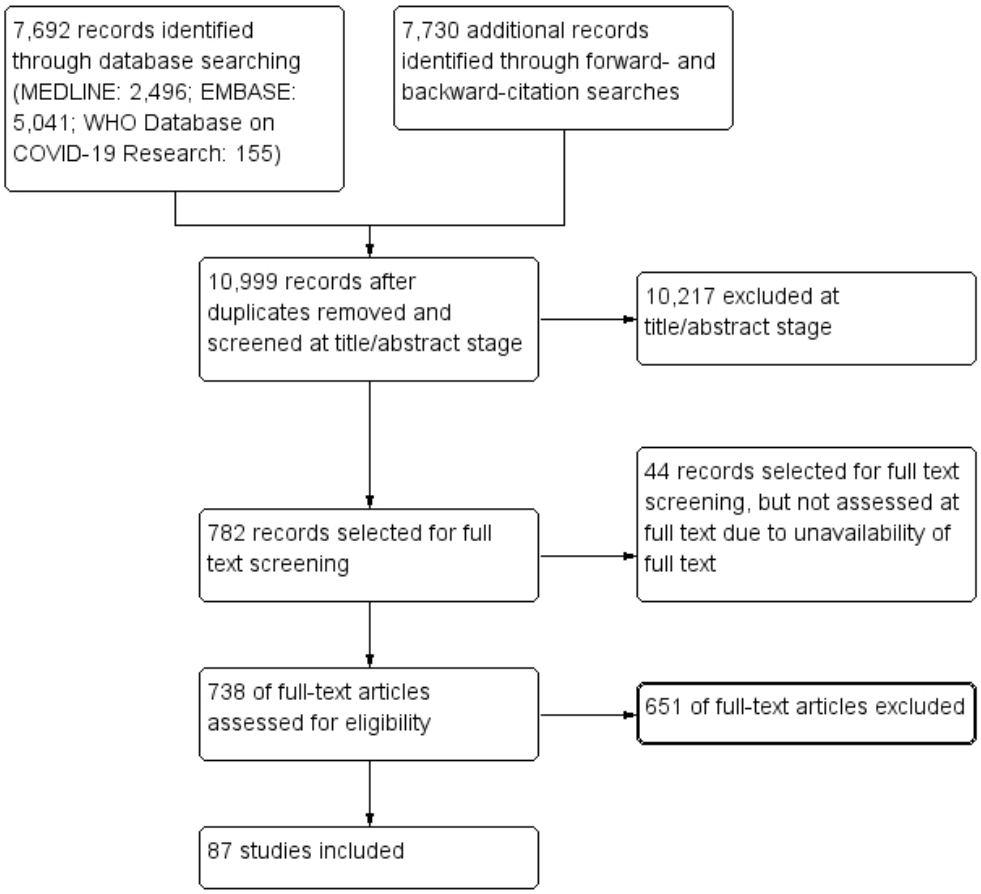

PRISMA flow chart

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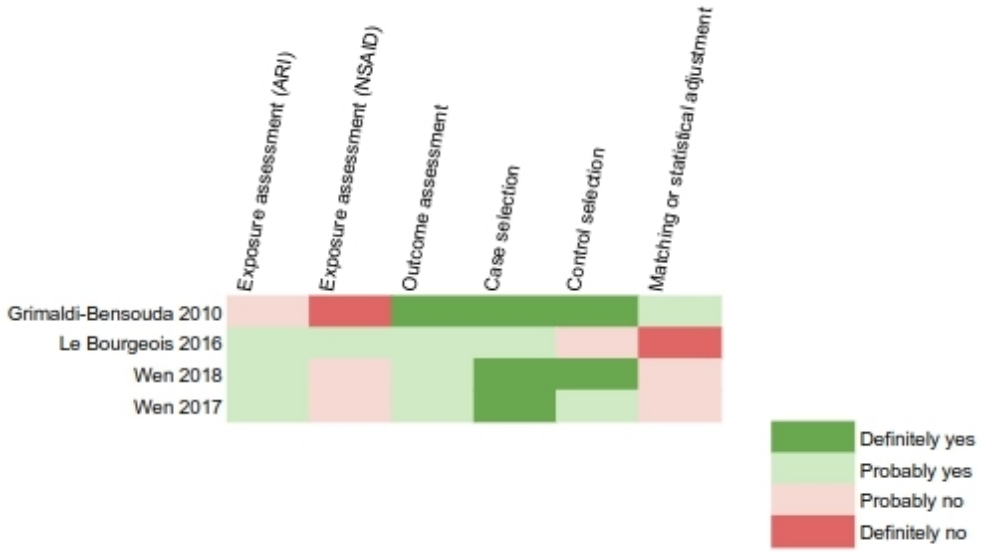

Risk of bias of case-control and case-crossover studies

132x82mm (96 x 96 DPI)

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Risk of bias of studies other than case-control and case-crossover studies

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Study protocol as registered with PROSPERO.

Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs) in COVID-19 and other viral respiratory infections: rapid review

Peter von Philipsborn, Renke Biallas, Jake Burns, Simon Drees, Karin Geffert, Movsisyan Ani, Lisa Pfadenhauer, Kerstin Sell, Brigitte Strahwald, Jan Stratil, Eva Rehfuess

Citation

Peter von Philipsborn, Renke Biallas, Jake Burns, Simon Drees, Karin Geffert, Movsisyan Ani, Lisa Pfadenhauer, Kerstin Sell, Brigitte Strahwald, Jan Stratil, Eva Rehfuess. Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs) in COVID-19 and other viral respiratory infections: rapid review. PROSPERO 2020 CRD42020176056 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020176056

Review question

What are the effects of prior and current use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with acute viral respiratory infections on acute severe adverse events (including mortality, acute respiratory distress syndrome (ARDS), acute organ failure and opportunistic infections), acute healthcare utilization (including hospitalization, intensive care unit (ICU) admission, supplemental oxygen therapy and mechanical ventilation), as well as on quality of life and long-term survival.

Searches

We will perform searches in MEDLINE and EMBASE, using the Ovid search interface. We will use existing reviews, key publications and included studies to perform backward- and forward-citation searches in Scopus. In addition, the review team will also screen the results of WHO's daily searches on COVID-19 in international databases and the results of daily focused searches in Chinese databases.

Our search strategy is based on two sets of search terms (NSAIDs, and viral respiratory infections), and was reviewed by an experienced information specialist (Dr Irma Klerings). All searches will be conducted in English and abstracts screened in English only. Database searches will be limited to studies published in English or German. For studies on the current Covid-19 outbreak, which will be provided to the review team by the World Health Organization (WHO), studies in English, French, German and Italian will be considered, and studies published in Chinese will be sent to WHO for translation into English and subsequently assessed by the review team. No restriction based on the year of publication will be applied. The MEDLINE and EMBASE search strategies, as well as the reviews and key publications used for the backward- and forward-citation searches are shown in the attached search strategy.

Search strategy

https://www.crd.york.ac.uk/PROSPEROFILES/176056_STRATEGY_20200323.pdf

Types of study to be included

Any systematic empirical study design (e.g., randomized controlled trials, cohort studies, case-control studies, case series >10 patients, case series with <10 patients (only for COVID-19, SARS, and MERS).

Condition or domain being studied

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 inflammations of infectious and non-infectious etiology. NSAIDs include unselective cyclooxygenase (COX) inhibitors (such as ibuprofen, aspirin (acetylsalicylate), diclofenac and naproxen) as well as selective COX 2 inhibitors (such as Celecoxib, Rofecoxib, Etoricoxib, Lumiracoxib, and Valecoxib).

Concerns have been raised that NSAIDs may be associated with an increased risk for adverse effects when used in patients with acute viral respiratory infections, including COVID-19 (caused by the virus SARS-CoV-2), Severe Acute Respiratory Syndrome (SARS, caused by SARS-CoV), Middle East Respiratory Syndrome (MERS, caused by MERS-CoV), and other coronavirus infections. These concerns apply both to the use of NSAIDs prior to the infection, and to the use of NSAID during the infection.

Participants/population

Humans of any age with acute viral respiratory infections, with or without chronic co-morbidities (e.g. cardiovascular disease, diabetes mellitus, COPD, asthma).

Intervention(s), exposure(s)

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).

Comparator(s)/control

No or different NSAID

Main outcome(s)

- Acute severe adverse events (e.g., mortality, acute respiratory distress syndrome, acute organ failure, cardiovascular events, opportunistic infections, severe acute allergic and hypersensitivity reactions);
- Acute healthcare utilization (e.g., rate and length of hospitalization, rate and length of intensive care unit utilization, rate and length of supplemental oxygen therapy, rate, length and type of mechanical ventilation);
- Longer term effects (e.g., explicit quality of life measures, long-term survival).

**** Measures of effect***

Any

Additional outcome(s)

- Laboratory measures, e.g., C-reactive protein (CRP), ferritin, leukocyte counts and others.
- Imagin/radiologic findings, e.g., CT chest scan, chest x-ray and others.

**** Measures of effect***

Any

Data extraction (selection and coding)

After removal of duplicate studies, we will perform a multistage screening process to select those studies which meet the inclusion criteria:
• Stage 1, screening of titles and abstracts: One review author will assess the titles and abstracts of all identified records. 20% of all titles and abstracts will be independently assessed by a second review author. Depending on the number of additional eligible studies identified by the second review author, we will decide if the remaining titles and abstracts will also be screened by a second review author.
• Stage 2, screening of full-texts: One review author will assess the full texts of all identified records selected in step 1. In cases deemed unclear or ambiguous by the first review author, advice from a second review author will be sought. 20% of all full texts will be independently assessed by a second review author. Depending on the number of additional eligible studies identified by the second review author, we will decide if the remaining full texts will also be screened by a second reviewer.

One review author will extract study characteristics and study data to the data extraction form. A second review author will check for completeness and correctness.

The data extraction form was pilot tested with four studies by four review authors, and adapted on this basis. As detailed in this extraction form, we will extract information on all primary outcomes, i.e. acute severe adverse events, acute healthcare utilization, long term survival and quality of life as detailed under inclusion criteria above. In addition, where available and time permitting, we will also extract information on the secondary outcomes (listed above).

One review author will assess all data extraction forms and classify NSAIDs based on their mechanism of action (unselective cyclooxygenase inhibitors, and selective cyclooxygenase 2 inhibitors).

Risk of bias (quality) assessment

One review author will assess risk of bias of included studies using the Cochrane risk of bias tool adapted by the Cochrane Effective Practice and Organization of Care (EPOC) group for non-randomised studies. It includes the following criteria:
1. Random sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Similarity of baseline outcome measurements (selection bias)
4. Similarity of other baseline characteristics (selection and performance bias)
5. Incomplete outcome data (attrition bias)
6. Blinding (performance and detection bias)
7. Contamination (performance bias)
8. Selective reporting (reporting bias)
9. Other potential sources of bias

We will use GRADE to assess the certainty of evidence of primary outcomes. The assessment of the certainty of evidence will be done by one review author, and the findings discussed among the core review team.

In GRADE, the certainty of evidence is the extent to which one can be confident that the true effect of an intervention lies on one side of a specified threshold, or within a chosen range. Within the GRADE approach, the certainty of evidence is assessed based on a number of factors which can decrease or increase the level of evidence. Traditionally, evidence from RCTs starts as high-certainty evidence in GRADE, and evidence from all other study designs starts as low-certainty.

Strategy for data synthesis

We will summarize the findings of the included studies narratively and with tables. If we find two or more sufficiently homogenous studies, we will conduct meta-analyses and present forest plots.

As much as possible within the timeframe and sensible in terms of the number of studies identified, we will conduct stratified analyses based on the following criteria:
• Pathogen/disease group (COVID-19, SARS, MERS, other coronaviruses, other viral respiratory infections)
• Age (elderly > 65 years, adults 18-65 years; adolescents 12-17 years, children 6-12 years, <6 years)
• Sex
• Severity of the acute viral respiratory infection (mild, moderate, severe)
• With or without acute respiratory distress syndrome (ARDS)
• Co-morbidities (pre-existing cardiovascular disease (including hypertension and ischemic heart disease), chronic obstructive pulmonary disease (COPD), asthma, diabetes mellitus, renal disease, rheumatic diseases, prior allergic or hypersensitive reactions to NSAIDs including Reye's syndrome)
• Type of NSAID used (unselective COX inhibitors, selective cyclooxygenase 2 inhibitors)
• Specific substance used (e.g. ibuprofen, aspirin, etc.) and dose (high vs. low)
• Prior use (incl. short-term/intermittent vs. chronic/long-term) vs. use during acute viral respiratory infection

All data presented in the final review manuscript in the narrative synthesis, in tables or in meta-analyses and forest plots will be independently checked by a second review author.

Analysis of subgroups or subsets

Not planned.

Contact details for further information

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Type and method of review

Intervention, Systematic review

Anticipated or actual start date

19 March 2020

Anticipated completion date

21 April 2020

Funding sources/sponsors

None.

Conflicts of interest

Language

English

Country

Germany

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Anti-Inflammatory Agents, Non-Steroidal; COVID-19; Drug-Related Side Effects and Adverse Reactions; Humans; Iatrogenic Disease; Respiratory Tract Infections; Virus Diseases; severe acute respiratory syndrome coronavirus 2

Date of registration in PROSPERO

24 March 2020

Date of first submission

23 March 2020

Stage of review at time of this submission

Stage	Started
Preliminary searches	Yes
Piloting of the study selection process	Yes
Formal screening of search results against eligibility criteria	Yes
Data extraction	No
Risk of bias (quality) assessment	No
Data analysis	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

24 March 2020

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Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with viral respiratory infections: Rapid review

Supplementary appendix

Peter von Philipsborn, Renke Biallas, Jacob Burns, Simon Drees, Karin Geffert, Ani Movsisyan, Lisa M. Pfadenhauer, Kerstin Sell, Brigitte Strahwald, Jan M. Stratil, Eva A. Rehfuess

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1. Search strategy for MEDLINE

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)** 1946 to March 19, 2020

Search Strategy:

#	Searches	Results
1	exp Anti-Inflammatory Agents, Non-Steroidal/	195828
2	exp cyclooxygenase Inhibitors/	127691
3	exp cyclooxygenase 2 Inhibitors/	13390
4	nsaid*.mp.	25230
5	((non-steroid* or nonsteroid* or non steroid*) adj2 (anti-inflammator* or antiinflammator* or anti inflammator*)).mp.	86055
6	(aceclofenac or acemetacin or carbasalate calcium or clonixin or dexibuprofen or etoricoxib or flufenamic acid or lornoxicam or loxoprofen or lumiracoxib or lysine acetylsalicylate or mefenamic acid or niflumic acid or parecoxib or rofecoxib or salsalate).mp.	10270
7	(tiaprofenic acid or tolfenamic acid or valdecoxib).mp.	1267
8	apazone.mp.	173
9	aspirin.mp.	66455
10	celecoxib.mp.	6850
11	ibuprofen.mp.	14692
12	diclofenac.mp.	12990
13	diflunisal.mp.	796
14	etodolac.mp.	679
15	fenoprofen.mp.	492
16	flurbiprofen.mp.	2655
17	indometacin.mp.	893
18	indomethacin.mp.	42523
19	ketoprofen.mp.	4277
20	ketorolac.mp.	3118
21	Meclofenamic.mp.	1146
22	meclofenamate.mp.	977
23	meloxicam.mp.	2184
24	meloxicam.mp.	2184
25	nabumetone.mp.	489
26	naproxen.mp.	6844
27	nimesulide.mp.	1703
28	oxaprozin.mp.	162
29	phenylbutazone.mp.	7171
30	piroxicam.mp.	3942
31	sulindac.mp.	2057
32	tenoxicam.mp.	622
33	tolmetin.mp.	1449
34	**or/1-33**	**256116**

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35	exp Coronavirus/	11361
36	exp Coronavirus Infections/	9639
37	(Coronavir* or Corona virus or covid* or Middle East Respiratory Syndrome or MERS or Severe Acute Respiratory Syndrome or SARS or nCov* or HCoV*).mp.	24300
38	exp Severe Acute Respiratory Syndrome/	4460
39	**or/35-38**	**25948**
40	exp Influenza, Human/	48266
41	exp Influenzavirus A/	43175
42	exp Influenzavirus B/	4211
43	(influenza* not h?em?phil* influenza*).ti,ab,kf.	95703
44	(flu or H1N1 orH2N2 or H3N2 or H1N12 or H5N1).ti,ab,kf.	24523
45	**or/40-44**	**111043**
46	exp Common Cold/	4184
47	common cold*.ti,ab,kf.	3955
48	coryza.ti,ab,kf.	643
49	upper respiratory infection*.mp.	2670
50	exp upper respiratory tract infection/	352313
51	viral respiratory tract infection*.mp.	385
52	urti.ti,ab,kf.	855
53	viral respiratory infection.mp.	261
54	(respiratory adj2 virus).mp.	18936
55	(respiratory adj2 viral).mp.	4736
56	Rhinitis/	12478
57	rhinitis.ti,ab,kf.	27388
58	exp Pharyngitis/	15528
59	pharyngitis.ti,ab,kf.	5754
60	RSV.mp.	11711
61	exp Nasopharyngitis/	432
62	nasopharyngitis.ti,ab,kf.	961
63	exp Laryngitis/	3984
64	laryngitis.ti,ab,kf.	2041
65	respiratory syncytial virus.mp.	14116
66	exp respiratory syncytial virus/	8670
67	exp rhinovirus/	3677
68	rhinovirus*.mp.	6170
69	(vir* adj2 pneumonia).ti,ab,kf.	2521
70	exp Pneumonia, Viral/	5512
71	parainfluenza virus 1, human/	2839
72	parainfluenza virus 3, human/	1152
73	**or/46-72**	**404261**
74	(respiratory distress syndrome or ARDS or lung injury).ti,ab,kf.	50457
75	exp Respiratory Distress Syndrome, Adult/	18986
76	**or/74-75**	**55783**

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77	(virus or viral).ti,ab,kf.	818649
78	**76 and 77**	**1683**
79	**39 or 45 or 73 or 78**	**478967**
80	**34 and 79**	**3761**
81	exp animals/ not humans/	4680615
82	**80 not 81**	**3048**
83	(english or german).lg.	26997379
84	**82 and 83**	**2496**

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2. Search strategy for EMBASE

Database(s): **Embase** 1974 to 2020 March 19
Search Strategy:

#	Searches	Results
1	exp nonsteroid antiinflammatory agent/	724205
2	nsaid*.mp.	45078
3	((non-steroid or nonsteroid or non steroid or non steroids) adj2 (antiinflammatory or antiinflammatory or anti inflammator)).mp.	121352
4	apazone.mp.	8
5	(aceclofenac or acemetacin or carbasalate calcium or clonixin or dexibuprofen or etoricoxib or flufenamic acid or lornoxicam or loxoprofen or lumiracoxib or lysine acetylsalicylate or mefenamic acid or niflumic acid or parecoxib or rofecoxib or salsalate or tiaprofenic acid or tolfenamic acid or valdecoxib).mp.	32918
6	azapropazone/	1157
7	aceclofenac/ or acemetacin/ or carbasalate calcium/ or clonixin/ or dexibuprofen/ or etoricoxib/ or flufenamic acid/ or lornoxicam/ or loxoprofen/ or lumiracoxib/ or lysine acetylsalicylate/ or mefenamic acid/ or niflumic acid/ or parecoxib/ or rofecoxib/ or salsalate/ or tiaprofenic acid/ or tolfenamic acid/ or valdecoxib/	31857
8	exp acetylsalicylic acid/	207229
9	aspirin.mp.	116112
10	celecoxib/	21891
11	celecoxib.mp.	22410
12	exp diclofenac/	39567
13	diclofenac.mp.	41365
14	diflunisal/	2736
15	diflunisal.mp.	2824
16	etodolac/	2697
17	etodolac.mp.	2752
18	fenoprofen/	2666
19	fenoprofen.mp.	2885
20	flurbiprofen/	7633
21	flurbiprofen.mp.	8192
22	exp ibuprofen/	49352
23	ibuprofen.mp.	51294
24	indometacin/	77047
25	indomethacin.mp.	41931
26	ketoprofen/	13036
27	ketoprofen.mp.	13592
28	ketorolac/	9703
29	ketorolac.mp.	11659
30	meclofenamic acid/	2804
31	meclofenamate.mp.	1447
32	meloxicam/	7073

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33	meloxicam.mp.	7290
34	nabumetone/ or nabumetone.mp.	2035
35	naproxen/ or naproxen.mp.	26999
36	nimesulide/ or nimesulide.mp.	4832
37	oxaprozin/ or oxaprozin.mp.	750
38	phenylbutazone/ or phenylbutazone.mp.	12841
39	piroxicam/ or piroxicam.mp.	11676
40	sulindac/ or sulindac.mp.	7587
41	tenoxicam/ or tenoxicam.mp.	2102
42	tolmetin/ or tolmetin.mp.	2688
43	**or/1-42**	**746194**
44	coronaviridae/	890
45	coronavirinae/	1047
46	exp coronavirus infection/	11075
47	coronavir*.mp.	18736
48	ncov*.mp.	310
49	covid*.mp.	6588
50	middle east respiratory syndrome.mp.	2678
51	mers.mp.	4610
52	severe acute respiratory syndrome.mp.	9798
53	sars.mp.	10912
54	HCoV*.mp.	690
55	**or/44-54**	**35940**
56	(respiratory distress syndrome or ARDS or lung injury).ti,ab.	71093
57	exp adult respiratory distress syndrome/ or exp acute lung injury/	46394
58	**or/56-57**	**84601**
59	(virus or viral).ti,ab.	926277
60	**58 and 59**	**3110**
61	exp influenza/	83750
62	(influenza* not (h?em?phil* influenza* or "h influenza*")).mp.	137610
63	flu.ab,ti.	19582
64	(h1n1 or h5n1 or h3n2).mp.	39113
65	**or/61-64**	**147898**
66	exp common cold/	8004
67	common cold*.ti,ab.	4466
68	coryza.ti,ab.	586
69	upper respiratory infection*.ti,ab.	3956
70	upper respiratory tract infection/	27635
71	urti.ti,ab.	1372
72	rhinit*.ti,ab.	39318
73	rhinitis/	18800
74	pharyngitis/	15196
75	pharyngit*.ti,ab.	7144

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76	rhinopharyngitis/	12432
77	laryngitis/	3672
78	laryngit*.ti,ab.	1987
79	nasopharyngit*.ti,ab.	2472
80	**or/66-79**	**109716**
81	(virus or viral).mp.	1487387
82	**80 and 81**	**13487**
83	rhinovirus.ti,ab.	6844
84	exp rhinovirus/	8285
85	vir* pneumonia.ab,ti.	1760
86	exp virus pneumonia/	14441
87	exp viral respiratory tract infection/	3869
88	exp parainfluenza virus infection/	1261
89	exp Human respiratory syncytial virus/	4427
90	respiratory syncytial virus.mp.	19005
91	**or/83-90**	**42933**
92	**55 or 60 or 65 or 82 or 91**	**213662**
93	**43 and 92**	**6543**
94	animal/ not human/	1061398
95	**93 not 94**	**6525**
96	(english or german).lg.	29902747
97	**95 and 96**	**6214**
98	**limit 97 to (article or article in press or erratum or letter or note or "review" or short survey)**	**5041**

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3. Search strategy for the WHO COVID-19 Research Database

We searched titles and abstracts with the following combination of search terms: “nsaids or nsaid or steroid or steroidal or nonsteroid or nonsteroidal anti-inflammatory or antiinflammatory or cyclooxigenase or aceclofenac or acemetacin or carbasalate calcium or clonixin or dexibuprofen or etoricoxib or flufenamic or lornoxicam or loxoprofen or lumiracoxib or acetylsalicylate or mefenamic or niflumic or parecoxib or rofecoxib or salsalate or tiaprofenic or tolfenamic or valdecoxib or apazone or aspirin or celecoxib or ibuprofen or diclofenac or diflunisal or etodolac or fenoprofen or flurbiprofen or indometacin or indomethacin or ketoprofen or ketorolac or Meclofenamic or meclofenamate or meloxicam or meloxicam or nabumetone or naproxen or nimesulide or oxaprozin or phenylbutazone or piroxicam or sulindac or tenoxicam or tolmetin or adverse or side effect or side effects or iatrogenic or harm or harmful or safe or safety”

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4. References used for forward- and backward-citation searches

References used for the first round of forward- and backward-citation searches

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References used for the second round of forward- and backward-citation searches

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References used for the third round of forward- and backward-citation searches

For the third round of forward- and backward-citation searches we used the references of all studies included based on the database searches and the first and second rounds of forward- and backward-citation searches (n=73), as well as the references of the following reviews:

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5. Data extraction form

Items of the data extraction form for studies in adults:

Study information:

- Reviewer initials
- Study ID
- Study title
- Publication year
- Study design
- Study length

Inclusion criteria:

- Study in humans?
- Empirical data?
- Study size?
- NSAID exposure?
- Viral respiratory infection?
- Relevant outcome?
- Link between NSAID, viral infection, and outcome?
- Comments

Population:

- Short verbal description of the population
- Total number of participants
- Disease/pathogen class
- Disease(s)
- Pathogen(s)
- Share of participants with a viral respiratory infection
- Severity of disease
- ARDS
- Underlying or pre-existing conditions, co-morbidities
- Age group
- Mean age
- Sex
- Ethnicity
- Country
- Comments

Intervention and comparison:

- Drug(s)
- Application
- Dosage and length of application
- Reason for the use or administration of NSAID
- Prescription vs. Over-the-counter (OTC) use
- NSAID used prior to or initiated during the viral respiratory infection
- Comparison
- Comments

Risk of bias assessment:

- Random sequence generation
- Allocation concealment
- Similarity of baseline outcome measures
- Similarity of baseline characteristics
- Incomplete outcome data
- Blinding
- Contamination
- Selective reporting
- Other risks of bias

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Outcomes (general):

- Severe acute adverse events?
- Healthcare utilization?
- Quality of life?
- Quote of all information on adverse outcomes reported in the study
- Type of AO reporting
- Details on how AO were assessed

Outcome (for specific outcome measures):

- Type of outcome
- Verbal summary of the outcome
- Verbal summary of the link between NSAID, viral infection, and outcome
- Follow-up
- Effect measure
- Total number of participants
- Outcome in the IG
- Participants in IG
- Outcome in the CG
- Participants in CG
- Summary RoB
- Comments

Items of the data extraction form for studies in children:

- Study ID
- Study title
- Study design
- Nr of participants
- Length of follow up
- Drugs used
- Disease / condition / pathogen
- Outcome measures

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6. Search log

Initial search	
Source	Nr. of hits
MEDLINE	2496
EMBASE	5041
First round of backward-citation search	1849
First round of forward-citation search	1183
Sum before de-duplication	10569
Sum after de-duplication	9047
Second round of backward- and forward-citation searches	
Second round of backward-citation search	359
Second round of forward-citation search	400
Sum before de-duplication	759
Sum after de-duplication	289
Third round of backward- and forward-citation searches	
Third round of backward-citation search	1319
Third round of forward-citation search	2620
Sum before de-duplication	3939
Sum after de-duplication	1508
WHO Database on Covid-19 research	
Initial search (March 25, 2020)	155
Excluded at title/abstract screening stage	148
Included for full text screening (this includes three studies in Chinese which we were unable to assess at full text)	7
Summary	
Total number of titles/abstracts screened (MEDLINE, EMBASE, Scopus, WHO Covid-19 database)	10999
Excluded at title/abstract screening stage	10196
Included at title/abstract screening stage and assessed at full text	738
Included at title/abstract screening stage, but not assessed at full text due to unavailability of full text	65
Excluded at full text screening stage	654
Included studies	84

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9. Characteristics of studies included in the evidence synthesis

Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
Azuma 2010	Japan	N: 170 adults Age range: 20-70 years Mean age: n.r. Disease: Upper respiratory tract infection (URTI)	Zaltoprofen, Placebo	Pain and fever relief	Dosage: Zaltoprofren 1: 160mg Zaltoprofren 2: 80mg Application: oral Frequency: once	RCT	6 hours	Counts of Adverse Effects (AEs): Symptoms after administration of study medication
Azuma 2011	Japan	N: 330 adults Mean age: Zaltoprofen: 33 years Loxoprofen: 36 Placebo: 36 Age range: 20-70 years Disease: Febrile URTI	Zaltoprofen, Loxoprofen, Placebo	Pain and fever relief	Dosage: Zaltoprofen: 160 mg Loxoprofen: 60mg Application: oral Frequency: once	RCT	4 hours	Counts of AEs: Symptoms after administration of study medication
Bachert 2005	Russia	N: 392 adults Age range: 18 - 65 years Mean age: 37.4 years Disease: Febrile URTI	Aspirin, Acetaminophen, Placebo	Pain and fever relief	Dosage: Aspirin 1: 500mg Aspirin 2: 1000mg Acetaminophen 1: 500mg Acetaminophen 2: 1000mg Application: oral Frequency: once	RCT	6 hours	Counts of (severe) AEs
Bettini 1986	Italy	N: 120 adults Age range: n.r. Mean age: 37 years Disease: Influenza-related fever	Diclofenac, Aspirin	Fever relief	Dosage: 1) Diclofenac 25 mg 2) Aspirin 500 mg Application: oral Frequency: 1) every 12 hours for two days 2) every 8 hours for two days	RCT	2 days	Count of AEs: Medication side effects
Boureau 1999	France	N: 113 adults Age range: 18-60 years	Ibuprofen, Paracetamol	Symptom relief	Dosage: Ibuprofen: 400mg Paracetamol: 1000mg	RCT	48 hours	Counts of AEs: symptoms after

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Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
		Mean age: n.r. Disease: Tonsillitis			Application: oral Frequency: once			administration of study medication
Broggini 1986	Italy	N: 30 adults Age range: n.r. Mean age: Flurbiprofen 34.4 years; Aspirin 41.6 years Disease: Influenza	Flurbiprofen, aspirin	Symptom relief	Dosage: 1) Flurbiprofen 2) aspirin Application: oral Frequency: twice daily over four days	RCT	4 days	Count of AEs: Medication side effects
Ebel 1985	USA	N: 312 adults Age range: 18 - 70 years Mean age: male: 38.5 years female 43.5 Disease: URTI	Sulindac, Placebo	Symptom relief	Dosage: Sulindac 200mg Application: n.r. Frequency: twice per day, 7 days	RCT	7 days	Counts of (severe) AEs
Eccles 2003	Sweden, UK	N: 279 adults Age range: 18-60 years Mean age: IG 25.5 years CG 24.5 years Disease: URTI	Acetylsalicylic Acid, Placebo	Symptom relief	Dosage: 400mg ASA Application: oral Frequency: 1-2 tablets every 4-6 hours for 3 days	RCT	3 days	Counts of AEs: Medication side effects
Eccles 2013	UK	N: 833 participants Age range: n.r. Mean age: n.r. Disease: URTI	Aspirin + Pseudoephedrine, Aspirin, Pseudoephedrine, Placebo	Symptom relief	Dosage: 1) 500 mg ASA + 30 mg PSE 2) 500 mg ASA 3) 60 mg PSE Application: oral Frequency: 2-3 doses on day 1, 3 doses for another 3 days	RCT	7 days	Counts of AEs
Epperly 2016	USA	N: 683 adults 838 children; Age range: n.r.	NSAIDs, Aspirin, non-use	Improvement of the medical	Dosage: n.r. Application: most likely oral intake Frequency: n.r.	Retrospective regi stry-	Adults: 60 days Children: 90	Risk of mortality

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Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
		Mean age: Adult NSAID user: 42.0 years; Adult non-user: 45.6 Adult aspirin user: 51.2 years Adult non-user: 44.1 Child NSAID user: 7.9 years non-user: 7.1 Disease: pH1N1		course of influenza		based cohort study	days	
Gehanno 2003	France	N: 343 Age range: 20-60 years Mean age: 40 years Disease: Febrile sore throat	Diclofenac potassium, Paracetamol	Pain and fever relief	Dosage: Diclofenac potassium 6.25 mg, 12.5 mg and 25 mg Paracetamol: 1000 mg Application: Oral Frequency: Once	RCT	10 days	Counts of AEs
Goto 2007	Japan	N: 189 Age group: 18-65 years Mean age: Loxoprofen: 29.3 years, Placebo 27.6 years Disease: URTI-like symptoms of the nose and pharynx	Loxoprofen, Placebo	Symptom relief	Dosage: Loxoprofen 60 mg Application: oral Frequency: 2-3 times a day for at most 7 days	RCT	7 days	Counts of AEs
Graham 1990	Australia	N: 60 adults Age range: 18 - 30 years Mean age: n.r. Disease: URTI	Aspirin, Acetaminophen, Ibuprofen	Symptom relief	Dosage: Aspirin: 500mg Acetaminophen: 500mg Ibuprofen: 200mg Application: Oral Frequency: Daily for 7 days Aspirin: 4 doses Acetaminophen: 4 doses Ibuprofen: 3 doses	RCT	28 days	Counts of AEs: Symptoms after administration of study medication
Grebe 2003	Germany	N: 356 adults Age range: ≥ 18 years	Diclofenac-K, Ibuprofen,	Symptom relief	Dosage: Diclofenac-K: 12.5mg, multiple, flexible dosing regimen	RCT	3 days	Counts of AEs

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Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
		Mean age: 40.2 years Disease: Influenza-like symptoms	Placebo		Ibuprofen: 200mg tablets multiple, flexible dosing regimen Application: oral Frequency: 3 days			
Grimaldi-Bensouda 2010	France	N: 177 children Age range: 2 months - 16 years Mean age: n.r. Disease: Fever, pain, rheumatic indication	Ibuprofen, Aspirin, non-use	Relief of fever	Dosage: Ibuprofen: 18 mg/kg Aspirin: 24 mg/kg Fenamates: 32m g/kg Ketoprofen: 2 mg/kg Flurbiprofen: 2 mg/kg Naproxen: 11.5 mg/kg Application: most likely oral Frequency: Daily, Mean duration of use: 1.9±1.5 days	Case-cross-over study	7 days	Risk of upper gastrointestinal bleeding
Grunthal 2008	Germany	N: 2341 Age range: n.r. Mean age: ca. 40 years Disease: Cold	acetylsalicylate (aspirin) + pseudoephedrin, paracetamol + caffeine + chlorphenamine maleat+ vitamin C	Symptom relief	Dosage: 1) acetylsalicylate (aspirin) (500mg) + pseudoephedrin (30mg) 2) paracetamol (200mg) + caffein (25mg) 3) chlorphenamin maleat (2,5 mg) + vitamin C (150 mg) Application: oral Frequency: 1) mean: 1.6 doses 2) mean: 1.9 doses	Cohort study	3 days	Counts of AEs
Hung 2017	Hong Kong	N: 217 adults Age range: ≥ 18 years Median: 80 years Disease: Influenza A (H3N3)	Clarithromycin + Naproxen + Oseltamivir, Oseltamivir	Treatment of severe influenza	Dosage: 1) triple combination (Clarithromycin 500 mg + Naproxen 200 mg + Oseltamivir 75 mg) 2) Oseltamivir 75 mg Application: oral Frequency:	RCT	30 days	Risk for Mortality (at 30 / 90 days), duration of hospitalization

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Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
					Group 1: 1) twice daily for two days and 2) twice daily for three days Group 2: 2) twice daily for five days			
Le Bourgeois 2016	USA	N: 166 children Age range: 3 -15 years Mean age: Cases: 4.1 ± 2.3 Controls: 3.8 ± 2.3 Disease: Acute viral infection (upper respiratory tract viral infections, lower respiratory tract viral infections and others)	Ibuprofen, Ketoprofen, non-use	Relief of symptoms	Dosage: n.r. Application: n.r. Frequency: 1, 2 and 3 consecutive days intake of Ibuprofen or Ketoprofen	Matched case-control study	Cases and controls: 15 days (retrospective)	Risk of hospitalization (empyema)
Lesko 1995	USA	N: 83,915 children Age range: 6 months - 12 years Mean age: n.r. Disease: Febrile illness	Ibuprofen, Paracetamol	Relief of symptoms of febrile illness	Dosage: Ibuprofen 1: 5mg/kg Ibuprofen 2: 10mg/kg Paracetamol: 10 mg/kg Application: oral Frequency: Ibuprofen 1 and 2: median number of doses 6-10, median duration 3 days	Randomized Controlled Trial (RCT)	4 weeks	Risk of hospitalization for acute gastrointestinal bleeding, acute renal failure, anaphylaxis or Reye's syndrome Counts of other (severe) AEs leading to hospitalization
Lesko 1997	USA	N: 288 children Age range: 6 months - 12 years	Ibuprofen, Acetaminophen	Relief of symptoms of	Dosage: Ibuprofen 1: 5mg/kg Ibuprofen 2: 10mg/kg	RCT	4 weeks	Risk of renal impairment

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Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
		Mean age: n.r. Disease: Febrile illness		febrile illness	Acetaminophen: 12mg/kg Application: oral Frequency: All: median number of doses 7, median duration 2 days			
Lesko 1999	USA	N: 27,065 children Age range: 1 - 23 months Mean age: n.r. Disease: Febrile illness	Ibuprofen, Acetaminophen	Relief of symptoms of febrile illness	Dosage: Ibuprofen 1: 5mg/kg Ibuprofen 2: 10mg/kg Acetaminophen: 12mg/kg Application: oral Frequency: All: median number of doses 6-10, median duration 3 days	RCT	4 weeks	Risk of hospitalization for acute gastrointestinal bleeding, acute renal failure, anaphylaxis or Reye's syndrome Counts of other (severe) AEs leading to hospitalization
Lesko 2002	USA	N: 1879 children Age range: 6 months - 12 years Mean age: n.r. Disease: Febrile illness	Ibuprofen, Acetaminophen	Relief of symptoms of febrile illness	Dosage: Ibuprofen 1: 5mg/kg Ibuprofen 2: 10mg/kg Acetaminophen: 12mg/kg Application: Oral Frequency: n.r.	RCT	4 weeks	Risk of outpatient visits or hospitalization for asthma
Little 2013	UK	N: 89 children and adults Age range: ≥ 3 years Mean age: Ibuprofen 34; Paracetamol 34; Both 33 Disease: Respiratory infections	Ibuprofen, Paracetamol, Ibuprofen + Paracetamol	Symptom relief	Dosage: n.r. Application: Oral Frequency: Dependent on trial arm; Regular dosing: 4x daily; As required dosing: as required by symptoms up to 4x daily	RCT	28 days	Healthcare utilization: return visit with new or worsening symptoms or complicationsof

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Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
		(upper and lower)						intervention
Llor 2013	Spain	N: 416 Age range: 18-70 years Mean age: 45.1 years Disease: RTI	Ibuprofen, Amoxicillin-clavulanic acid, Placebo	Symptom relief	Dosage: Ibuprofen: 600 mg Amoxicillin-clavulanic acid: 500 mg Application: n.r. Frequency: 3 daily for 10 days	RCT	11-13 days	Counts of AEs: events possible related to drug
Loose 2011	Germany	N: 640 adults Age range: not reported Mean age: 19.6 years Disease: URTI leading to nasal congestion	Aspirin + Pseudoephedrine, Paracetamol + Pseudoephedrine, Placebo	Symptom relief	Dosage:a) ASA + 60mg PSE b) ASA + 30mg PSE c) Paracetamol 1000 mg +60mg PSE d) Placebo Application: oral Frequency: once	RCT	6 h	Counts of AEs
Milvio 1984	Switzerland	N: 50 adults Age range: n.r. Mean age: Nimesulide: 38 years; Benzydamine: 49 years Disease: Inflammation of the ear, nose and throat	Nimesulide, Benzydamine	Treatment of fever and inflammation	Dosage:1) Nimsulide 100 mg 2) Benzydamine 75 mg Application: oral Frequency: twice a day for 10 days	RCT	10 days	Count of AEs: Medication side effects
Nouri 1993	Austria or Switzerland	N: 65 adults Age range: 35-62 years Mean age: IG: 39 years CG: 53 years Disease: Non-bacterial inflammation of the ear, nose and throat	Nimesulide, Naproxen	Treatment of inflammation	Dosage: 1) Nimseluide 100 mg 2) Naproxen 500 mg Application: oral Frequency: Twice daily, mean duration 8.7 days	RCT	10 days	Counts of AEs

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Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
Ottaviani 1993	Italy	N: 940 children and adults Age range: 15-77 years Mean age: 38 years Disease: URTI or Otitis media	Nimesulide	Symptom relief	Dosage: Nimesulide 100 mg Application: oral Frequency: twice a day for or a mean (± SD) of 10 (± 4) days	Cohort study	10 days	Counts of AEs
Schachtel 1988	USA	N: 120 adults Age range: 18 - 88 years Mean age: Ibuprofen: 41.5 years, Acetaminophen: 46.1 Disease: Severe throat pain	Ibuprofen, Acetaminophen, Placebo	Symptom relief	Dosage: Ibuprofen: 400mg Acetaminophen: 1000mg Application: oral Frequency: Once	RCT	1 day	Counts of AEs
Schachtel 1991	USA	N: 210 adults Age range: 18 - 83 years Mean age: 30 Disease: Tonsillopharyngitis/URTI	Aspirin + caffeine, Aspirin, Placebo	Pain relief	Dosage: Aspirin 1: 800mg + 64mg Aspirin 2: 800mg Placebo Application: oral Frequency: Once	RCT	2 hours	Counts of AEs
Schachtel 2007	USA	N: 197 adults Age range: ≥ 18 years Mean age: n.r. Disease: Tonsillopharyngitis	Valdecoxib, Placebo	Symptom relief	Dosage: Valdecoxib 1: 40 mg Valdecoxib 2: 20 mg Placebo Application: n.r. Frequency: once	RCT	24 hours	Counts of AEs
Schachtel 2011	USA	N: 269 adults Age range: 18 - 30 Mean age: 19 Disease: Sore throat	Celecoxib, Placebo	Pain relief	Dosage: Celecoxib 1: 50-mg + 50 mg after 6-12 hours Celecoxib 2: 100-mg + placebo after 6-12 hours Celecoxib 3: 100-mg + 50 mg after 6-12 hours Placebo: placebo + placebo after	RCT	24 hours	Counts of AEs

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Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
					6-12 hours Application: oral Frequency: once			
Smith 2014	USA	N: 207 adults Age range: 18 - 34 years Mean age: 21 years Disease: URTI	Ibuprofen + Caffeine, Ibuprofen, Caffeine, Placebo	Symptom relief	Dosage: Ibuprofen + Caffeine: 200mg + 100mg Ibuprofen: 200mg Caffeine: 100mg Placebo Application: Oral Frequency: once	RCT	3 hours	Counts of AEs
Sperber 1989	USA	N: 58 adults Age range: n.r. Mean age: 20-21 years Disease: Cold	Ibuprofen + Pseudoephedrine, Pseudoephedrine Placebo	Symptom relief	Dosage: Pseudoephidrine + Ibuprofen: 60mg + 200mg Pseudoephidrine 60mg Placebo Application: Oral Frequency: 2 doses the first day, 4 doses over next 4 days	RCT	14 days	Counts of AEs: symptoms after administration of study medication
Sperber 1992	USA	N: 87 adults Age range: n.r Mean age: 21.4 years Disease: Cold	Naproxen, Placebo	Symptom relief	Dosage: See below Application: oral Frequency: Naproxen 1: 1 loading dose (400mg) + 3 times daily 200mg for 5 days Naproxen 2 and 3: 1 loading dose (500mg) + 3 times daily 500mg for 5 days	RCT	5 days	Counts of AEs
Wen 2017	Taiwan	N: 9,793 adults Age range: >20 years	NSAID, No NSAID	Pain and fever relief	Dosage: n.r. Application: n.r.	Case-Crossove	Cases: 7 days	Risk of myocardial infarction

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Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
		Mean age: 72.3 years at diagnosis Disease: Acute respiratory infection (ARI			Frequency: n.r.	r Study		
Wen 2018	Taiwan	N: 29,518 adults Age range: > 20 years Mean age: 73.4 years Disease: Acute respiratory infection (ARI)	NSAID (any single-active-ingredient NSAIDs, non-use	Pain and fever relief	Dosage: n.r. Application: n.r. Frequency: n.r.	Case-Crossover Study	Cases: 7 days	Risk for ischemic and hemorrhagic stroke
Weckx 2002	Brazil, Colombia and Mexico	N: 357 adults Age range: ≥ 18 years Mean age: Celecoxib once daily: 32 Celecoxib twice daily: 31 Diclofenac: 32 Disease: Viral pharyngitis	Celecoxib, Diclofenac	Symptom relief	Dosage: 1) Celecoxib 200 mg 2) Diclofenac 75 mg Application: oral Frequency: a) 1) once daily b) 1) twice daily, c) 2) twice daily for five days	RCT	5 days	Counts of (serious) AEs
Younkin 1983	USA	N: 47 children and adults Age range: 17-20 years Mean age: n.r. Disease: Influenza	Aspirin, Amantadine		Dosage: Aspirin: 325 mg Amantadine 1: 100mg Amantadine 2: 100mg Application: Oral Frequency: For 5 days Aspirin: 10 daily Amantadine 1: 1 daily Amantadine 2: 1 daily	RCT	7 days	Count of AEs: Medication side effects

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10. Effects on primary outcomes reported by studies included in the evidence synthesis

Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
Comparison of NSAID use with no NSAID use: Effects on mortality				
Epperly 2016	NSAIDs use vs. non-use	Risk for mortality	NSAID use: Risk: 22.7% Non-use: Risk: 24.2% aRR = 0.9 (0.5-1.6)	Effects on mortality of NSAID in adults with H1N1 influenza are unclear. The confidence interval of the effect estimate is large, and includes the possibility of a positive, null or negative effect.
Epperly 2016 (subgroup analyses)	Aspirin use vs. non-use	Risk for mortality	Aspirin use: Risk: 23.8% Non-use: Risk: 24.1% aRR = 1.1 (0.6-1.9)	Effects on mortality of aspirin in adults with H1N1 influenza are unclear. The confidence interval of the effect estimate is large, and includes the possibility of a positive, null or negative effect.
NSAID use vs. no NSAID use: Effects cardiovascular events				
Wen 2017	NSAIDs vs. non-use	Risk for myocardial infarction	NSAID during ARI: aOR = 3.41; (2.80-4.16) ARI without NSAID: aOR = 2.65; (2.29-3.06) NSAID use only: aOR = 1.47 (1.33-1.62) No exposure (reference): aOR = 1	NSAID use in individuals with an acute respiratory infection (ARI) was associated with a higher odds ratio for myocardial infarction compared to: a) individuals with an ARI not exposed to NSAIDs, b) individuals without an ARI exposed to NSAIDs, c) individuals without an ARI not exposed to NSAIDs. Confidence intervals overlap, indicating that the effect of NSAID in patients with ARI on risk for myocardial infarction is unclear. The confidence intervals include the possibility of a positive, null or negative effect.
Wen 2018	NSAIDs vs. non-use	Risk for ischemic stroke	NSAID use during ARI: aOR = 2.27; (2.00-2.58) ARI without NSAID use: aOR = 2.11; (1.91-2.34) NSAID use only: aOR = 1.38 (1.30-1.46) No exposure (reference): aOR	NSAID use in individuals with an acute respiratory infection (ARI) was associated with a higher odds ratio for ischemic stroke compared to: a) individuals with an ARI not exposed to NSAIDs, b) individuals without an ARI exposed to NSAIDs, c) individuals without an ARI not exposed to NSAIDs. Confidence intervals overlap, indicating that the effect of NSAID in patients with ARI on risk for ischemic stroke is unclear. The confidence intervals include the

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Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
			= 1	possibility of a positive, null or negative effect.
Wen 2018	NSAIDs vs. non-use	Risk for hemorrhagic stroke	NSAID during ARI: aOR = 2.28; (1.71-3.02) ARI without NSAID: aOR = 1.63; (1.31-2.03) NSAID use only: aOR = 1.49 (1.31-1.69) No exposure (reference): aOR = 1	NSAID use in individuals with an acute respiratory infection (ARI) was associated with a higher odds ratio for hemorrhagic stroke compared to: a) individuals with an ARI not exposed to NSAIDs, b) individuals without an ARI exposed to NSAIDs, c) individuals without an ARI not exposed to NSAIDs. Confidence intervals overlap, indicating that the effect of NSAID in patients with ARI on risk for hemorrhagic stroke is unclear. The confidence intervals include the possibility of a positive, null or negative effect.
Multiple comparisons: Effects on adverse event counts				
Azuma 2010	Zaltoprofen vs zaltoprofen vs placebo	Counts of severe adverse events (SAEs)	Not explicitly reported	That study reports several mild adverse events, and explicitly states that no severe adverse events occured (Quote: "Three headaches, 2 odynophagias and 2 joint pain cases occurred in the 80-mg group. One odynophagia, 1 joint pain, 1 muscle pain, 1 glutamic oxaloacetic transaminase (GOT) increase and 1 lactate dehydrogenase (LDH) increase occurred in the 160-mg group. All of these events were mild.")
Azuma 2011	Zaltoprofen vs loxoprofen vs placebo	Counts of SAEs	Not explicitly reported	That study reports with regard to observed adverse events that "[t]hese were mostly mild symptoms, and no unknown adverse events were encountered." Moreover, the study reports that "[n]o significant differences existed in the incidence of adverse events among groups." (Full quote: "In the present study, adverse events were seen in 8 of 131 patients (6.1%) in the zaltoprofen group, in 4 of 131 patients (3.1%) in the loxoprofen group, and in 9 of 60 patients (15.0%) in the placebo group. (…) These were mostly mild symptoms, and no unknown adverse events were encountered. In the zaltoprofen group, cases included 1 patient (0.8%) with tonsillitis aggravation, 1 patient (0.8%) with orthostatic hypotension, 1 patient (0.8%) with asthmatic attack, and 2 patients (1.5%) with exanthema/itch sensation. In the loxoprofen group, they included 1 patient (0.8%) with joint pain, 1 patient (0.8%) with urinary protein, and 1 patient (0.8%)

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Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
				with hives.")
Bachert 2005	Aspirin vs acetaminophen (paracetamol) vs placebo	Counts of SAEs	Aspirin: 0 SAEs Acetaminophen: 0 SAEs Placebo: 0 SAEs	The study reports that "[n]o serious or severe adverse events were reported."
Bettini 1986	Diclofenac sodium vs aspirin	Counts of SAEs	Not explicitly reported	The study reports that ["a]s regards side effects, episodes of slight epigastric pain were recorded in one patient treated with Novapirina and in five patients treated with Aspirin. No patient had to discontinue the treatment because of side effects."
Boureau 1999	Ibuprofen vs Paracetamol	Counts of SAEs	Not explicitly reported	The study reports that "[t]here were no serious adverse effects and no statistically significant difference in the incidence of adverse events in the two treatment groups", but provides only very little detail on whether and how SAEs were monitored or reported.
Broggini 1986	Flurbiprofen vs aspirin	Counts of SAEs	Not explicitly reported	The study reports that "[s]ide effects were reported by two cases on ASA (1 dyspepsia necessitating withdrawal of treatment and 1 bitter taste) and 3 cases on flurbiprofen (1 heartburn, 1 drowsiness and 1 nausea)."
Ebel 1985	Sulindac vs placebo	Counts of SAEs	Sulindac: 0 SAEs Placebo: 0 SAEs	The study reports that "[n]one of the adverse experiences reported was rated serious."
Eccles 2003	Aspirin + pseudo-ephedrine vs aspirin; Aspirin + pseudo-ephedrine vs pseudoephedrine; Aspirin + Pseudo-ephedrine vs placebo	Counts of SAEs	Aspirin + pseudoephedrine: 0 SAEs Aspirin: 0 SAEs Pseudoephedrine: 0 SAEs Placebo: 0 SAEs	The study reports that "[n]o serious adverse events were reported."

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Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
Eccles 2013	Aspirin + pseudo-ephedrine vs aspirin; Aspirin + pseudo-ephedrine vs pseudoephedrine; Aspirin + Pseudo-ephedrine vs placebo	Counts of SAEs	Aspirin + pseudoephedrine: 1 SAE Aspirin: 0 SAEs Pseudoephedrine: 0 SAEs Placebo: 0 SAEs	Study reports that "[o]verall one serious adverse event (SAE) occurred. The patient was treated with aspirin plus PSM [pseudoephedrine]. The SAE was a fall, and feeling faint after the fall." The study also notes that "[t]he investigator considered that the fall and the faint feeling were not related to the study drug."
Gehanno 2003	Diclofenac potassium vs Paracetamol	Counts of SAEs	Diclofenac potassium 6.25 mg: 0 SAEs Diclofenac potassium 12.5mg: 0 SAEs Diclofenac potassium 25 mg: 0 SAEs Paracteamol: 0 SAEs	The study reports that the patients reporting any AEs did not differ significantly between study groups. Additionally, they report that "[n]o patients had to be withdrawn from the study because of an adverse experience. There were no serious adverse experiences and no deaths during the trial."
Goto 2007	Loxoprofen vs placebo	Counts of SAEs	Not explicitly reported	The study reports that "[e]ight patients in the loxoprofen group (9.5%) complained of several kinds of adverse events including drowsiness (in three) and thirst (in two) during the follow-up period, which was higher than the one patient in the placebo group (1.1%) with drowsiness."
Graham 1990	Aspirin vs acetaminophen (paracetamol) vs ibuprofen vs placebo	Counts of SAEs	Not explicitly reported	The study does not report explicitly on SAEs, but reports that "the aspirin group experienced more side effects than the other groups. Five in the aspirin group did not complete the full course of medication, because of tinnitus in all 5 cases and gastrointestinal symptoms in 1 of those; they stopped on days 3 and 4. Despite stopping medication, these volunteers continued to participate and completed all other aspects of the study."
Grebe 2003	Diclofenac-K vs ibuprofen vs placebo	Counts of SAEs	Diclofenac-K: 0 SAEs Ibuprofen: 0 SAEs Placebo: 0 SAEs	The study reports that "no serious treatment-related adverse events were reported."

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Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
Grunthal 2008	Acetylsalicylate (aspirin) + pseudoephedrin vs paracetamol + caffeine + chlorphenamine + vitamin C	Counts of SAEs	Not explicitly reported	The study reports that 4.8% of participants receiving paracetamol and 9.8% of participants receiving aspirin reported side effects, which were "mostly of mild or moderate severity". The most common side effects in the aspirin group were "gastric pain, upper abdominal pain and nausea".
Hung 2017	Clarithromycin + naproxen + oseltamivir vs oseltamivir	Counts of SAEs	Not explicitly reported	The study notes that "no patient in our study reported adverse events due to drug-drug interaction." The study does not report explicitly whether and how SAEs were monitored or reported.
Llor 2013	Ibuprofen vs Amoxicillin-clavulanic acid vs Placebo	Counts of SAEs	Ibuoprofen: 0 SAEs amoxicillin-clavulanic acid: 1 SAE Placebo: 0 SAEs	The study reports that AEs were more common in the Aamoxicillin-clavulanic acid group than in the Ibuprofen or placebo groups. The only SAE in recorded in the study, a digestive haemmorrhage requiring admission to the intensive care unit, occurred in the amoxicillin-clavulanic acid group.
Loose 2004	Aspirin + pseudoephedrinevs aspirin + pseudoephedrine + placebo vs acetaminophen (paracetamol) + pseudoephedrine + placebo vs placebo	Counts of SAEs	Aspirin + pseudoephedrine: 0 SAEs Aspirin + pseudoephedrine + placebo: 0 SAEs Paracetamol + pseudoephedrine + placebo: 0 SAEs Placebo: 0 SAEs	The study reports that "[d]uring the study, 153 adverse events (AEs) in 113/645 (17.5 %) patients were reported or observed. All of these events were non-serious. "
Milvio 1984	Nimesulide vs benzydamine	Counts of SAEs	Not explicitly reported	The study reports that "[n]imesulide was generally very well tolerated. Only one patient suffered from moderate gastric pyrosis and drowsiness."
Nouri 1993	Nimesulide vs	Counts of SAEs	Not explicitly reported	The study notes that "[t]herapy with nimesulide was well tolerated and was not

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Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
	Naproxen			associated with adverse reactions. In the naproxen group, however, 2 patients experienced episodic gastralgia of moderate intensity, one starting on the third, and the other on the eighth day of therapy. Laboratory parameters were not modified by either treatment."
Ottaviani 1993	Nimesulide	Counts of SAEs	Nimesulide: 10 SAEs out of 940 patients	The study reports that „[t]he drug was well tolerated, and of the 75 patients who reported adverse effects, only 26 had to be withdrawn from treatment. (…) Physicians' assessments of therapeutic efficacy and tolerability of treatment were good in most patients". The SAEs reported included „[w]ater retention, sweating, flush, loss of appetite, vision disturbance, (…) [h]eartburn, gastralgia, dyspepsia, nausea, (…) [v]ertigo, (…) [r]ash [and] urticaria."
Schachtel 1988	Ibuprofen vs acetaminophen (paracetamol) vs placebo	Counts of AEs	Not explicitly reported	The study reports that "[n]o adverse effects were reported during the study." The study provides only very little detail on whether and how SAEs were monitored.
Schachtel 1991	Aspirin vs placebo	Counts of SAEs	Not explicitly reported	The study reports that "[o]f the 210 patients admitted to the study, one patient (receiving aspirin) was discontinued after 1 hour because of an adverse effect (nausea and vomiting) (…). There were no other side effects or exclusions from the trial."
Schachtel 2007	Valdecoxib vs placebo	Counts of SAEs	Valdecoxib (high dose): 0 SAEs Valdecoxib (low dose): 0 SAEs Placebo: 0 SAEs	The study reports that "[t]here were no serious adverse events, and no patient discontinued the study as a result of an adverse event."
Schachtel 2011	Celecoxib vs Celecoxib + Placebo vs Placebo	Counts of SAEs	Celecoxib (low dose + low dose): 0 SAEs Celecoxib (low dose + high dose): 0 SAEs	The study reports that "[t]here were no serious AEs, deaths, or discontinuations due to an AE. Overall, the incidence of AEs was similar among the 4 treatment groups."

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Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
			Celecoxib (low dose) + Placebo: 0 SAEs Placebo: 0 SAEs	
Smith 2014	Ibuprofen + caffeine vs ibuprofen vs caffeine vs placebo	Counts of SAEs	Not explicitly reported	The study reports that "[t]here were no serious adverse events reported, and studymedication was well tolerated."
Sperber 1989	Pseudoephidrine + ibuprofen vs pseudoephidrine vs placebo	Count of SAEs	Not explicitly reported	The study notes that both drugs "were generally well tolerated. No subjects withdrew from the study due to adverse drug effects." The study mentions the following "possible adverse effects of treatment": "Lightheadedness, Difficulty sleeping, Lethargy, Indigestion".
Sperber 1992	Naproxen vs placebo	Counts of SAEs	Not explicitly reported	The study reports that "[s]ide effects to naproxen were not noted in any of the three cohorts. One volunteer in the naproxen group experienced gastrointestinal symptoms after two doses of the drug, but after missing two doses, completed treatment without incident. Two volunteers receiving placebo had gastrointestinal complaints."
Weckx 2002	Celecoxib (1x daily) vs celecoxib (2x daily) vs diclofenac	Counts of SAEs	Celecoxib (1x): 0 SAEs Celecoxib (2x): 0 SAEs Diclofenac: 0 SAEs	Study reports that "[n]o serious adverse events were recorded."
Younkin 1983	Apsirin vs amantadine (1x daily) vs amantadine (2x daily)	Counts of SAEs	Not explicitly reported	The study reports that "[a] number of volunteers in all groups experienced a symptomatic complaint on at least one occasion that they attributed to the medication. In the aspirin treatment group, the subjects took all tablets, but six did not take all prescribed capsules. All subjects took all medications the first 3 days of the study. Six patients also had at least one episode of insomnia, nausea, or tinnitus."

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Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
Comparison of ibuprofen with acetaminophen (paracetamol): Effects on the rate of reconsultations				
Little 2013	Ibuprofen vs Paracetamol vs Ibuprofen + Paracteamol	Healthcare utilization: return visit with new or worsening symptoms or complicationsof intervention	Ibuprofen risk of reconsultation: 20%; Paracetamol risk of reconsultation: 12%; Ibuprofen + Paracetamol risk of reconsultation: 17% aRR(Ibuprofen vs Paracetamol) = 1.67 (1.12-2.38)	For the outcome reconsultation (with new or unresolved symptoms or complications within one month), the study reports 35/300 (11%) events in the paracetamol group, 58/295 (20%) in the ibuprofen group and 48/285 (17%) for the combined ibuprofen/paracetamol group. The adjusted risk ratio for the ibuprofen vs. the paracetamol group was 1.67 (95% CI: 1.12 to 2.38; p-value: 0.012). The study reports that "[m]ost of the 17 "complications" recorded were not serious, and three could be classified as reconsultations based on the baseline case record form."

11. Characteristics of and outcomes reported in studies included in the evidence mapping

Study ID	Study title	Study design	Partici-pants (n)	Follow up	Drugs	Disease / pathogen	Adverse outcome reporting	Reporting on adverse outcomes
Aksoylar 1997	Evaluation of sponging and antipyretic medication to reduce body temperature in febrile children	RCT	224	3 hours	Sponging alone vs. Sponging with a single oral dose of aspirin 15 mg/kg, or paracetamol 15 mg/kg, or ibuprofen 8 mg/kg	URTI, Pneumonia, Otitis media, gastroenteritis, UTI, Others	The study explicitly reports that there were no severe adverse outcomes;	"No serious side effects were observed that required stopping the treatment."

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Autret 1997	Evaluation of ibuprofen versus aspirin and paracetamol on efficacy and comfort in children with fever	RCT	351	5 days	Ibuprofen vs. Aspirin vs. Paracetamol	Fever	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"Of the 348 patients included, 14 patients experienced 18 adverse effects. […] In the ibuprofen group, 9 patients reported 13 adverse effects, 1 of which was experienced twice. In the paracetamol group, one child had one adverse effect and in the aspirin group four patients had four adverse effects."
Autret-Leca 2007	Ibuprofen versus paracetamol in pediatric fever: objective and subjective findings from a randomized, blinded study	RCT	301	3 days	Acetaminophen vs. Ibuprofen	Fever	The study explicitly reports severe adverse outcomes;	"All adverse events reported were either mild or moderate in severity. One serious adverse event was reported in a patient after having taken seven doses of randomized treatment (paracetamol) on the first day. The child was suffering from persistence of wavering fever and onset of cough – an X-ray revealed pneumopathy. The child recovered 4 days later but withdrew from the trial. The event was recorded as having no relationship to study drug."
Barberi 1993	Double-Blind Evaluation of Nimesulide vs Lysine-Aspirin in the Treatment of Paediatric Acute Respiratory Tract Infections	RCT	70	5 days	Nimesulide vs. Lysine-aspirin	Acute infection and inflammation of the respiratory tract (laryngitis, tracheitis, bronchitis, pneumonia)	The study explicitly reports on mild or moderate adverse outcomes, but does	"Gastrointestinal adverse events were observed in 11 patients (3 treated with nimesulide and 8 treated with lysine-aspirin), but none required withdrawal from therapy. In addition, no significant changes in laboratory

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							not mention severe adverse outcomes;	tests were observed with either drug (p >0.05)."
Bertin 1991	Randomized, double-blind, multicenter, controlled trial of ibuprofen versus acetaminophen (paracetamol) and placebo for treatment of symptoms of tonsillitis and pharyngitis in children	RCT	231	48 hours	Ibuprofen vs. Acetaminophen and placebo	Sore throat related to tonsillitis or pharyngitis	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"Twelve children had mild side effects: five of these were in the Placebo group (nausea, abdominal pain, and two cutaneous rashes), three of these were in the acetaminophen group (nausea), and five of these were in the ibuprofen group (nausea and abdominal pain). No other side effects were reported. Treatment was never interrupted because of side effects."
Cappella 1993	Efficacy and Tolerability of Nimesulide and Lysine Acetylsalicylate in the Treatment of Paediatric Acute Upper Respiratory Tract Inflammation	RCT	70	4.5 days	Nimesulide vs. Lysine-acetylsalicylate	URTI and fever	The study explicitly reports that there were no adverse outcomes (without specifying their severity);	"There were no relevant adverse effects observed during treatment or significant changes in the haematological profile in any patient."

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Choi 2018	The antipyretic efficacy and safety of propacetamol compared with dexibuprofen in febrile children: a multicenter, randomized, double-blind, comparative, phase 3 clinical trial	RCT	311	3 days	Propacetamol vs. Dexibuprofen	Fever due to URTI	The study explicitly reports that there were no severe adverse outcomes;	"A total of 84 adverse events in 64/263 patients were reported. Adverse events included vomiting, diarrhea, abdominal pain, constipation, rash, elevated liver enzyme, and thrombocytopenia. [...] There were no serious adverse events in which the patient(s) had been exposed to a danger to life, required a longer hospital stay, or had acquired permanent or major sequalae."
Erlewyn-Lajeunesse 2006	Randomised controlled trial of combined paracetamol and ibuprofen for fever	RCT	123	1hour	Paracetamol vs. Ibuprofen vs. Both	Fever	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	One child experienced a rapid temperature drop from 39.5°C to 37.7°C in one hour. She was admitted for observation and recovered spontaneously. “One child in the paracetamol group received a dose of 27.8 mg/kg in error. The child did not suffer any adverse consequences from this overdose. There were no other adverse events.”
Figueras Nadal 2002	Effectiveness and tolerability of ibuprofen-arginine versus paracetamol in children with fever of likely infectious origin	RCT	187 ITT	8 hours	Ibuprofen + arginine vs. Paracetamol	Fever due to: Upper RTI, Lower RTI, Gastrointestinal infection, Upper UTI, Soft tissue Infection, Otitis, Other	The study explicitly reports that there were no severe adverse outcomes;	"Nineteen patients (9.5%) experienced a total of 19 adverse events, 10 of them in the ibuprofen-arginine group and 9 following paracetamol administration, with a mild to moderate intensity. No serious adverse events were reported within the study period. One patient presented with

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								neutropenia prior to the first intake of paracetamol and this was consequently considered as unrelated to the study medication."
Gelotte 2010	Multiple-Dose Pharmacokinetics and Safety of an Ibuprofen–Pseudoephedrine Cold Suspension in Children	Open-label safety study, uncontrolled	114	4 days	Ibuprofen-pseudoephedrine suspension	Rhinitis	The study explicitly reports that there were no severe adverse outcomes;	"A total of 18.4% (21/114) of subjects reported 1 or more adverse events; none were classified as serious. [...] Drug-related adverse events, that is, those that were classified by the investigator as definitely, probably, possibly, or of unknown relationship to study drug, were reported by 13.2% (15/114) of subjects (data not provided). All but 1 adverse event (cough increased) was mild or moderate in intensity."
Gianiorio 1993	Antipyretic and Anti-Inflammatory Efficacy of Nimesulide vs Paracetamol in the Symptomatic Treatment of Acute Respiratory Infections in Children	RCT	40	7 days	Nimesulide vs. Paracetamol	LRTI	The study explicitly reports that there were no adverse outcomes (without specifying their severity);	"No adverse reactions, abnormal physical findings or abnormal laboratory results attributable to either nimesulide or paracetamol were observed."
Goyal 1998	Double Blind Randomized comparative evaluation of nimesulide and paracetamol as antipyretics	RCT	99	3 days	Nimesulide vs. Paracetamol	Fever	The study explicitly reports on mild or moderate adverse	"Adverse reactions were seen in the form of epigastric pain and vomiting in one patient in nimesulide group and three patients in paracetamol group."

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							outcomes, but does not mention severe adverse outcomes;	
Hadas 2011	Premarketing Surveillance of Ibuprofen Suppositories in Febrile Children	Safety study, uncontrolled	490	7 days	Ibuprofen suppositories	Fever	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"Adverse reactions were reported in 8 patients (1.63%, 95% confidence interval = 1.77-3.25). The most common adverse event was diarrhea: 4 children (0.8%, 95% confidence interval = 0.24-2.2) had diarrhea immediately after the administration of the drug. Two children developed a rash, 1 child had shivering, and 1 child had rectal burning after suppository administration."
Hay 2008	Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): randomised controlled trials	RCT	156	5 days	Combination of paracetamol and ibuprofen vs. Paracetamol vs. Ibuprofen	Fever	The study explicitly reports severe adverse outcomes;	Parents recorded adverse effects. "The most common adverse effects were diarrhoea and vomiting, which were equally distributed between groups. The overall number of children experiencing adverse events was, however, too small to make meaningful comparisons between treatments. Five children were admitted to hospital (constituting serious adverse events)": PCM group: 1, ibuprofen group: 3, PCM plus ibuprofen group: 1 child.

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Jayawar-dena 2017	Antipyretic Efficacy and Safety of Ibuprofen Versus Acetaminophen Suspension in Febrile Children: Results of 2 Randomized, Double-Blind, Single-Dose Studies	RCT	333	8 hours	Ibuprofen vs. Acetaminophen	Fever	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"In total, 7.5% of patients in each treatment group had AEs. In the IBU group, 1 incidence each of headache, vomiting, and rash were considered related to the study drug. In the APAP group, 3 incidences of vomiting were considered related to the study drug."
Kandoth 1984	Comparative Evaluation of Antipyretic Activity of Ibuprofen and Aspirin in Children with Pyrexia of Varied Aetiology	Cross-over study	28	2 days	Ibuprofen vs. Aspirin	URTI, Bronchitis, Pyrexia of unknown origin, Malaria, Miscellaneous	The study explicitly reports that there were no adverse outcomes (without specifying their severity);	"In this single-dose study no side-effects were observed with either drug."

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Kauffman 1992	Antipyretic Efficacy of Ibuprofen vs Acetaminophen	RCT	38	24 hours	Ibuprofen vs. Acetaminophen vs. Placebo	Fever without apparent focus of infection (n=8); herpetic stomatitis (n=1); otitis media (n=7); acute pharyngitis (n=10); pneumonia (n=3); acute sinusitis (n=1); and viral upper respiratory tract infection (n=7)	The study explicitly reports that there were no adverse outcomes (without specifying their severity);	"No adverse reactions, abnormal physical findings, or abnormal laboratory results attributable to either ibuprofen or acetaminophen were observed."
Khalil 2017	A multicenter, randomized, open-label, active-comparator trial to determine the efficacy, safety, and pharmacokinetics of intravenous ibuprofen for treatment of fever in hospitalized pediatric patients	RCT	121	up to 5 days	Ibuprofen (intravenous) vs. Acetaminophen	Fever	The study explicitly reports severe adverse outcomes;	"Adverse events were reported for 54 of the 100 patients, with most (97%) being classified as mild to moderate in severity. [...] There were no deaths reported in this study. There were four (4%) subjects for whom six serious adverse events were reported. In the intravenous ibuprofen group, two subjects experienced four serious adverse events; one with pancreatitis and hepatitis and one with cardiac arrest and pneumothorax. In the acetaminophen group, two (2%) subjects experienced two serious adverse events; pleural effusion, and intra-abdominal abscess. None of the serious adverse events were deemed related to either intravenous ibuprofen or acetaminophen in the opinion of an independent

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								data safety monitor."
Kim 2013	Dexibuprofen for fever in children with upper respiratory tract infection	RCT	260	4 hours	Dexibuprofen (two different doses) vs. Ibuprofen	URTI	The study explicitly reports that there were no severe adverse outcomes;	"There were no significant differences in number of AE experienced (P = 0.98), nor were there differences in number of patients experiencing AE in each group (DEX 1, n = 33; DEX 2, n = 34; control, n = 35). When AE were classified according to severity (grades 1–5; data not shown), there were no differences in severity between the three groups. Of the 159 AE, all but three were grade 1 or 2. Of these three, two were fever and one was coughing."
Kramer 2008	Alternating Antipyretics: Antipyretic Efficacy of Acetaminophen Versus Acetaminophen Alternated With Ibuprofen in Children	RCT	36	6 hours	Ibuprofen alternated with acetaminophen vs. acetaminophen alone	Fever	The study explicitly reports on mild or moderate adverse	"During the study period, 8 (21%) of all patients had symptoms including diarrhea, flatulence, emesis, decreased appetite, epigastric pain, nausea, headache, and

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							outcomes, but does not mention severe adverse outcomes;	insomnia. These symptoms did not prevent any of the patients from taking the study medications. There were no differences between groups in the incidence of any of these potential side effects."
Lal 2000	Antipyretic effects of nimesulide, paracetamol and ibuprofen-paracetamol	RCT	89	5 days	Nimesulide vs. Paracetamol vs. Ibuprofen + paracetamol	URI and LRI	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"As far as the monitoring of other ADR was concerned, only a few adverse effects namely, epigastric pain, vomiting were encountered and on comparing it in different groups, no marked difference was found."
Lee 2015	Single intramuscular injection of diclofenac sodium in febrile pediatric patients	Cohort study	300	2 days	Diclofenac sodium	Febrile illness	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"One patient developed hypothermia 4 h following injection of diclofenac sodium" "no asthmatic attacks occurred in the emergency room during the observation" "Two patients with a history of asthmatic bronchitis had wheezing" "there were no reported allergic reactions"
Luo 2017	Alternating Acetaminophen and Ibuprofen versus Monotherapies in	RCT	474	24 hours	Acetaminophen + ibuprofen vs. Acetaminophen	Febrile illness (due to suppurative tonsillitis, URTI,	The study explicitly reports on	"No obvious toxicities were observed" "Asthma": 2/157 in ibuprofen

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	Improvements of Distress and Reducing Refractory Fever in Febrile Children: A Randomized Controlled Trial				vs. Ibuprofen	acute bronchitis, herp angina, hand foot and mouth disease, angina subitum)	mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	group vs 0/156 in paracetamol and 0/158 in alternating group"
Marriott 1991	A dose ranging study of ibuprofen suspension as an antipyretic	RCT	93	12 hours	Ibuprofen (4 different doses)	Fever	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"A total of 19 adverse clinical events were recorded in 17 children during the study periods. Five children vomited, seven children had behavioural changes ranging from 'more miserable' to 'delirious', there were five febrile convulsions (all in children admitted following a febrile convulsion), one child developed diarrhoea, and one child manifested a rash."
McIntyre 1996	Comparing efficacy and tolerability of ibuprofen and paracetamol in fever	RCT	150	3 days	Ibuprofen vs. Paracetamol	Febrile convulsion, viral illness (non-specific), chest infection, asthma/wheezing, croup, gastroenteritis, bronchiolitis, soft tissue infection, urinary tract infection, otitis media, tonsillitis, herpes stomatitis,	The study explicitly reports severe adverse outcomes;	"Seven patients in the ibuprofen group and eight in the paracetamol group withdrew due to adverse events and/or lack of efficacy." AE ibuprofen group: urticarial rash, vomiting, abdominal pain and sore throat, AE PCM group: nose bleed, purpuric spots at the site of the blood pressure cuff, and meningococcal meningitis. "Twenty four out of 150 patients (16%) experienced 34

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						septic arthritis, tracheitis, septicaemia		adverse events during the study: 10/76 patients (13%) in the ibuprofen group had 16 events and 14/74 patients (19%) in the paracetamol group had 18 events."
Nabulsi 2006	Alternating ibuprofen and acetaminophen in the treatment of febrile children: A pilot study	RCT; in regard to NSAID: cohort study	70	8 hours	Ibuprofen + acetaminophen vs. Ibuprofen + placebo	Febrile illness	The study explicitly reports that there were no severe adverse outcomes;	"No serious adverse reactions were observed in these subjects. In addition, none of the subjects developed any symptom or sign suggestive of gastrointestinal, hepatic or renal toxicity."
Polidori 1993	A Comparison of Nimesulide and Paracetamol in the Treatment of Fever Due to Inflammatory Diseases of the Upper Respiratory Tract in Children	RCT	110	6 days	Nimesulide vs. Paracetamol	Tonsillitis, Laryngitis, Pharyngitis, Otitis, Tracheitis, Bronchitis, Exanthema	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"Three patients treated with nimesulide and 6 patients treated with paracetamol withdrew from therapy because of urticaria, vomiting or diarrhoea."
Prado 2006	Antipyretic efficacy and tolerability of oral ibuprofen, oral dipyrone and intramuscular dipyrone in children: A randomized controlled trial	RCT	75	2 hours	Ibuprofen vs. Dipyrone (two different doses)	URI and LRI	The study explicitly reports on mild or moderate adverse outcomes, but does not	"There was only one case of mild, transient urticaria, which appeared 30 minutes after oral ibuprofen administration in a girl aged 9.1 months. [...] The urticaria remitted by the time of reaching three hours after ibuprofen administration, without any specific therapy."

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							mention severe adverse outcomes;	
Ruperto 2011	A randomized, double-blind, placebo-controlled trial of paracetamol and ketoprofren lysine salt for pain control in children with pharyngotonsillitis cared by family pediatricians	RCT	97	4 days	Paracetamol vs. Ketoprofen vs. Placebo	Pharyngotonsillitis	The study explicitly reports that there were no severe adverse outcomes;	"Safety evaluations at 1, 4 hours after administration was rated good or very good by parents, investigators and children in more than 90% of the cases for both paracetamol and placebo. No serious adverse events occurred. Four adverse events were observed in 4 patients: bronchitis and rash in the ketoprofen lysine salt group, diarrhoea and cough in the placebo group"
Salmon Rodriguez 1993	Assessment of the efficacy and safety of nimesulide vs naproxen in pediatric patients with respiratory tract infection	RCT	99	8 days	Nimesulide vs. Naproxen	Pharyngo-amygdalitis	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"In this study, more adverse events were observed with naproxen than with nimesulide." Most were gastrointestinal (4 nimesulide recipients and 13 naproxen recipients [$p < 0.05$, Chi^2-test]). "Several naproxen recipients reported more than 1 adverse event [...] Furthermore, urinalysis revealed a significant ($p = 0.04$) increase in proteinurea for patients treated with naproxen compared with those treated with nimesulide."
Sarrell 2006	Antipyretic treatment in young children with fever	RCT	480	14 days	Acetaminophen vs. Ibuprofen vs. Alternated acetaminophen	Fever due to: URI, AOM, Pharyngitis, Bronchiolitis, Gastroenteritis,	The study explicitly reports that there	"None of the patients in any of the groups had a drug-related adverse event or serious illness. Mild elevation in levels of liver

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					and ibuprofen	Viral illness	were no severe adverse outcomes;	enzymes and renal findings were observed in 8 children (1.7%) and 14 children (3.0%), respectively, but none of the acute-stage laboratory abnormalities persisted to the 14-day follow-up evaluation, and there were no statistically significant differences among the groups (P=.60 for abnormal liver function and P=.93 for abnormal renal function)."
Senel 2012	Comparison of Acetaminophen and Ketoprofen in Febrile Children: A Single Dose Randomized Clinical Trial	RCT	316	6 hours	Ketoprofen vs. Acetaminophen	Fever	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"In the present study only one patient had an allergy favoring urticaria in the ketoprofen group."
Sheehan 2016	Acetaminophen versus Ibuprofen in Young Children with Mild Persistent Asthma	RCT	300	46 weeks	Ibuprofen vs. Acetaminophen	Pain or fever	The study explicitly reports severe adverse outcomes	"No significant between-group differences were observed with respect to adverse events or serious adverse events. Six serious adverse events occurred in the acetaminophen group and 12 in the ibuprofen group. No deaths from any cause occurred during the trial."
Simila 1976	Oral Antipyretic Therapy: Evaluation of Ibuprofen	nRCT	79	6 hours	Ibuprofen vs. Indomethacin vs.	Fever mostly due to respiratory	The study explicitly	"No side effects from the drugs were seen in this series of

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					Aspirin vs. Paracetamol vs. Aminophenazone	infection	reports that there were no adverse outcomes (without specifying their severity)	patients."
Ugazio 1993	Clinical and pharmacokinetic study of nimesulide in children	RCT (not blinded)	100	up to 9 days	Nimesulide oral suspension vs. Paracetamol	Acute URTI and fever	The study explicitly reports that there were no adverse outcomes (without specifying their severity);	"there were no drug-related adverse events recorded"
Ulukol 1999	Assessment of the efficacy and safety of paracetamol, ibuprofen and nimesulide in children with upper respiratory tract infections	RCT (not blinded)	90	up to 5 days after discharge	Paracetamol, ibuprofen vs. Nimesulide	Acute URTI and fever	The study explicitly reports that there were no adverse outcomes (without specifying their severity);	"Paracetamol, ibuprofen and nimesulide were remarkably well tolerated and there were no drug-related side effects recorded, including haematological abnormalities and hepatotoxicity."
Van Esch 1995	Antipyretic Efficacy of Ibuprofen and Acetaminophen in Children With Febrile Seizures	RCT	71	24 hours	Ibuprofen vs. Acetaminophen	Febrile seizure	The study explicitly reports on mild or moderate	"Fourteen adverse events were recorded in nine patients. [Ibuprofen treatment: 6; acetaminophen treatment: 8 ....] The other adverse events

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							adverse outcomes, but does not mention severe adverse outcomes;	were [two] gastrointestinal complaints (acetaminophen), exanthemas [ibuprofen: 1, acetaminophen: 2], insomnia (ibuprofen), and hypothermia [ibuprofen: 2, acetaminophen: 1]."
Vauzelle-Kervroedan 1996	Antipyretic efficacy of tiaprofenic acid in febrile children	RCT	55	48 hours	Tiaprofenic acid vs. Placebo	Fever	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"Five (9.1%) children had vomited during the six hour period after dosing: 3 in the [placebo] group, and 2 in the TA group" [...] "No major side effect was reported by the parents during the study period"
Vauzelle-Kervroedan 1997	Equivalent antipyretic activity of ibuprofen and paracetamol in febrile children	RCT	116	2-4 days	Ibuprofen vs. Acetaminophen	Fever	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"Two children vomited during the study (1.7%), both of whom had received paracetamol."
Vyas 2014	Randomized comparative trial of efficacy of paracetamol,	RCT	99	4 hours	Paracetamol vs. Ibuprofen vs.	Upper respiratory infection, lower	The study explicitly	"No serious or severe adverse events were noted in any of the

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	ibuprofen and paracetamol-ibuprofen combination for treatment of febrile children				Combination	respiratory infection, viral illness, bronchiolitis	reports that there were no severe adverse outcomes;	groups. [...] In the ibuprofen group, three patients out of 32 had experienced the adverse events; one had nausea, one abdominal pain and one had maculopapular skin rash. All the three adverse events were mild with a possible relationship to treatment. In the combination group, four patients out of 31 had experienced the adverse events. One patient had vomiting, which was mild with doubtful relationship to treatment. Two patients had abdominal pain and one patient had a skin rash, which were mild with a possible relationship to treatment."
Walker 1986	Comarative Efficacy Study of Chewable Aspirin and Acetaminophen in the Antipyresis of Children	RCT	46	4 hours	Aspirin vs. Acetaminophen	Fever	The study explicitly reports that there were no adverse outcomes (without specifying their severity);	"Adverse effects were not observed with either drug."
Walson 1989	Ibuprofen, acetaminophen, and placebo treatment of febrile children	RCT	118	48 hours	Ibuprofen suspension vs. Acetaminophen elixir vs. Placebo liquid	Fever	The study explicitly reports on mild or moderate adverse	"The most common of all adverse experiences that appeared to be drug related (p= 0.07) were mild gastrointestinal symptoms. These occured in 10 of the 32 patients who received

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							outcomes, but does not mention severe adverse outcomes;	5 mg/kg ibuprofen, 6 of the 28 who received 10 mg/kg ibuprofen, 6 of the 33 who received 20 mg/kg acetaminophen, and 2 of the 34 patients who received placebo."
Walson 1992	Comparison of Multidose Ibuprofen and Acetaminophen Therapy in Febrile Children	RCT	64	48 hours	Ibuprofen vs. Acetaminophen	Fever	The study explicitly reports that there were no severe adverse outcomes;	Six children were withdrawn from the study, two because of dosing errors, three because of hypothermia (temperature of less than 35.6°C; all three patients were in the acetaminophen group), and one because of gastrointestinal distress (ibuprofen group). "No adverse effects of greater than moderate severity were reported."
Wilson 1991	Single-dose, placebo-controlled comparative study of ibuprofen and acetaminophen antipyresis in children	non-randomised trial	178	12 hours	Ibuprofen suspension vs. Acetaminophen elixir vs. Placebo suspension	Fever	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	One child had transient hypothermia and profuse night sweats due to pulmonary tuberculosis and a second child had a transient drop in temperature below 36.1°C
Wong 2001	Antipyretic effects of dipyrone versus ibuprofen versus acetaminophen in children: results of a	RCT	628	14 days	Dipyrone vs. Acetaminophen vs. Ibuprofen	Fever	The study explicitly reports on mild or	"Most of the adverse events were gastrointestinal in nature, such as vomiting and diarrhea. Of the total adverse events

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	multinational, randomized, modified double-blind study						moderate adverse outcomes, but does not mention severe adverse outcomes;	within each group, those considered drug-related comprised 17% of the dipyrone, 15% of the acetaminophen, and 27 % of the ibuprofen groups. There were no statistically significant differences among the three groups with respect to the incidence of adverse events."
Yilmaz 2003	Intramuscular Dipyrone versus Oral Ibuprofen or Nimesulide for Reduction of Fever in the Outpatient Setting	RCT	252	2 hours	Ibuprofen vs. Nimesulide, dipyrone	Fever	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"An erythematous eruption occurred in only one mpatient who used nimesulide. The number of cases where the axillary temperature dropped below 36°C was 15 (17.9%) in the diphyrone group, six (7.1%) in the ibuprofen group, and three (3.6%) in the nimesulide group."
Yoon 2008	The effects and safety of dexibuprofen compared with ibuprofen in febrile children caused by upper respiratory tract infection	RCT	255	3 days	Dexibuprofen (two different doses) vs. Ibuprofen	Fever due to URTI	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"In 255 children, 49 adverse drug reactions of mild to moderate level were reported in 32 children (12.7%) during the study [...] The adverse reactions included diarrhoea, constipation, nausea, vomiting, abdominal pain, decreased oral intake, irritability, facial oedema, skin rash, elevated liver enzyme level and thrombocytopenia"

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Yoshikawa 2001	Study of Influenza-Associated Encephalitis/Encephalopathy in Children During the 1997 to 2001 Influenza Seasons	Case series	20	Through disease course	Diclofenac sodium, acetaminophen, a combination of sulpyrine and acetaminophen, combination of acetaminophen and Mefenamic acid	Influenza	The study explicitly reports severe adverse outcomes;	Only children with influenza-associated encephalitis/encephalopathy were studied. "Concerning the use of antipyretics, no patient had taken apsirin before the onset. Sixteen patients had taken some antipyretics before the onset of encephalitis/encephalopathy. Eight patients had received diclofenac sodium rectally..." "With regard to the use of antipyretics, all 5 deceased patients were given antipyretics, 3 having taken diclofenac sodium.. Five of the 7 patients who fully recovered had taken antipyretics (ie, 3 diclofenac sodium and 2 acetaminophen)."

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12. Summary of Findings tables for children

Table s1: Use of NSAIDs vs. no use of NSAIDs in children with viral respiratory infections

Patient or population: children (between 2 months and 16 years) with viral respiratory infections
Intervention: use of NSAIDs
Comparison: no use of NSAIDs

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)*
Mortality H1N1 influenza Follow-up: up to 90 days following intensive care unit admission or until death or hospital discharge	**Epperly 2016** Risk associated with NSAIDs use: aRR = 1.5 (CI: 95%: 0.7-3.2)	838 (1 retrospective, registry-based cohort study)	⊕◯◯◯ VERY LOW [a]
Empyema Viral respiratory infections Follow-up: 15 days (from time of infection onset to empyema (cases) or to definition of control (controls))	**Le Bourgeois 2016** Risk associated with NSAIDs use: aOR = 2.79 (95% CI: 1.4-5.6)	166 (1 matched case-control study)	⊕◯◯◯ VERY LOW [b]
Acute gastrointestinal bleeding Viral respiratory infections Follow-up: 4 weeks (retrospective)	**Grimaldi-Bensouda 2010** Risk associated with NSAIDs use: aOR = 8.2 (95%CI: 2.6-26.0)	177 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]

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

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

Explanations
a. Downgraded evidence by 1 level for imprecision.
b. Downgraded evidence by 1 level for study limitations (risk of protopathic bias).

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Table s2: Use of ibuprofen vs. acetaminophen in children with fever

Patient or population: children (aged between 6 months and 12 years) with viral respiratory infections
Intervention: use of ibuprofen
Comparison: use of acetaminophen

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Death from any cause Follow-up: 4 weeks	**Lesko 1995** 1 death as consequence of car crash in acetaminophen group (1/28,130) 1 death from meningitis in the ibuprofen group (1/55,785)	83915 (1 RCT)	⊕⊕⊕⊕ HIGH
Hospitalization for any cause Follow-up: 4 weeks	**Lesko 1995** Relative risk of hospitalization for any cause: 0.99 (95% CI: 0.83-1.17)*	83915 (1 RCT)	⊕⊕⊕◯ MODERATE [a]
Acute gastrointestinal bleeding Follow-up: 4 weeks	**Lesko 1995** Risk of acute gastrointestinal bleeding in the ibuprofen group: 7.2 per 100 000 (95% CI: 2 to 18 per 100 000) Risk of acute gastrointestinal bleeding in the acetaminophen group: 0 per 100 000 (95% CI: 0 to 11 per 100 000)	83915 (1 RCT)	⊕⊕⊕◯ MODERATE [b]
Hospitalization for acute renal failure, anaphylaxis Follow-up: 4 weeks	**Lesko 1995** 0 events in either group	83915 (1 RCT)	⊕⊕⊕⊕ HIGH
Hospitalization for potentially serious adverse drug events (low white blood cell counts, erythema multiform, and serum sickness) Follow-up: 4 weeks	**Lesko 1995** Relative risk of hospitalization for potentially serious adverse drug events: 2.8 (95% CI: 0.61-12.5)*	83915 (1 RCT)	⊕⊕⊕◯ MODERATE [b]
Hospitalization for asthma Follow-up: 4 weeks	**Lesko 1995** Relative risk of hospitalization for asthma: 0.92 (95% CI: 0.56-1.52)*	83915 (1 RCT)	⊕⊕⊕◯ MODERATE [b]

***Calculations for this estimate were done by the review authors.**

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

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Explanations

a. Downgraded evidence by 1 level for study limitations: concerns for incomplete outcome reporting.

b. Downgraded evidence by 1 level for imprecision.

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12. Sub-group analyses

Table s3: Use of NSAIDs vs. no use of NSAIDs in adults with viral respiratory infections (subgroup analyses)

Patient or population: Adults with viral respiratory infections (Wen 2017; Wen 2018), adults with influenza (Epperly 2016)
Intervention: Use of NSAIDs
Comparison: No use of NSAIDs

Outcomes	Impact1	№ of participants (studies)	Certainty of the evidence (GRADE)2
1. Parenteral NSAIDs			
Ischemic stroke Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	**Wen 2018** Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 4.24 (95% CI: 2.92-6.15) risk associated with ARI episode: aOR = 2.11 (95% CI: 1.91 - 2.34) risk associated with NSAID use: aOR = 2.67 (95% CI: 2.23 - 3.20)	23618 (1 case-crossover study)	⨁◯◯◯ VERY LOW [a]
Hemorrhage stroke Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	**Wen 2018** Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 9.71 (95% CI: 3.79-24.92) risk associated with ARI episode: aOR = 1.66 (95% CI: 1.33 - 2.06) risk associated with NSAID use: aOR = 3.71 (95% CI: 2.57 - 5.33)	(5900 (1 case-crossover study)	⨁◯◯◯ VERY LOW [a]
Myocardial infarction Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	**Wen 2017** Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 7.22 (95% CI: 4.07-12.81) risk associated with ARI episode: aOR = 2.65 (95% CI: 2.29-3.07) risk associated with NSAID use: aOR = 3.77 (95% CI: 2.85-5.02)	9793 (1 case-crossover study)	⨁◯◯◯ VERY LOW [a]
2. High dose non-parenteral NSAIDs			
Ischemic stroke Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	**Wen 2018** Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 2.28 (95% CI: 1.76-2.95) risk associated with ARI episode: aOR = 2.11 (95% CI: 1.91 - 2.34) risk associated with NSAID use: aOR =1.26 (95% CI: 1.13 - 1.41)	(23618 (1 case-crossover study)	⨁◯◯◯ VERY LOW [a]

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Hemorrhagic stroke Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	**Wen 2018** Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 1.47 (95% CI: 0.85-2.52) risk associated with ARI episode: aOR = 1.66 (95% CI: 1.33 - 2.06) risk associated with NSAID use: aOR = 1.38 (95% CI: 1.09 - 1.76)	(5900 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
Myocardial infarction Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	**Wen 2017** Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 3.32 (95% CI: 2.34-4.93) risk associated with ARI episode: aOR = 2.65 (95% CI: 2.29-3.07) risk associated with NSAID use: aOR =1.10 (95% CI: 0.92-1.32)	9793 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
3. Low dose non-parenteral NSAIDs			
Ischemic stroke Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	**Wen 2018** Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 1.98 (95% CI: 1.70-2.32) risk associated with ARI episode: aOR = 2.11 (95% CI: 1.91 - 2.34) risk associated with NSAID use: aOR =1.28 (95% CI: 1.21 - 1.38)	(23618 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
Hemorrhagic stroke Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	**Wen 2018** Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 1.97 (95% CI: 1.39-2.79) risk associated with ARI episode: aOR = 1.66 (95% CI: 1.33 - 2.06) risk associated with NSAID use: aOR = 1.31 (95% CI: 1.13 - 1.52)	(5900 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
Myocardial infarction Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	**Wen 2017** Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 2.95 (95% CI: 2.31-3.75) risk associated with ARI episode: aOR = 2.65 (95% CI: 2.29-3.07) risk associated with NSAID use: aOR = 1.38 (95% CI: 1.23-1.54)	9793 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
4. Aspirin			
Mortality H1N1 Influenza Follow-up: 60 days following intensive care unit admission or until death or hospital discharge	**Epperly 2016** Mortality risk associated with aspirin use: aRR = 1.1 (95% CI: 0.6-1.9)	683 (1 retrospective, registry-based cohort study)	⊕◯◯◯ VERY LOW [b]
5. Diclofenac			

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Myocardial Infarction Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	**Wen 2017** Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 3.37 (95% CI: 2.24-5.07) risk associated with ARI episode: aOR = 2.65 (95% CI: 2.29-3.06) risk associated with NSAID use: aOR = 1.29 (95% CI: 1.06-1.58)	9793 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
6. Mefenamic acid			
Myocardial infarction Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	**Wen 2017** Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 3.11 (95% CI: 1.85-5.25) risk associated with ARI episode: aOR = 2.65 (95% CI: 2.29-3.06) risk associated with NSAID use: aOR = 1.65 (95% CI: 1.17-2.31)	9793 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
7. Coxibs			
Myocardial infarction Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	**Wen 2017** Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 2.90 (95% CI: 1.26-6.70) risk associated with ARI episode: aOR = 2.65 (95% CI: 2.29-3.06) risk associated with NSAID use: aOR = 1.43 (95% CI: 1.12-1.82)	9793 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
8. NSAIDs other than Coxibs, Mefenamic acid, or Diclofenac			
Myocardial infarction Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	**Wen 2017** Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 2.76 (95% CI:1.97-3.87) risk associated with ARI episode: aOR = 2.65 (95% CI: 2.29-3.07) risk associated with NSAID use: aOR = 1.18 (95% CI: 1.02-1.35)	9793 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
9. More than one NSAIDs			
Myocardial infarction Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	**Wen 2017** Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 3.37 (95% CI: 2.08-5.46) risk associated with ARI episode: aOR = 2.65 (95% CI: 2.29-3.07) risk associated with NSAID use: aOR = 1.62 (95% CI: 1.24-2.13)	9793 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]

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
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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

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Explanations

[1]All ORs reported for Wen 2017 and Wen 2018 are adjusted for discordant use of concomitant medications. ORs reported for Epperly 2016 are adjusted for age, sex, and vaccination and health status. [2]All studies included for this comparison were non-randomized; thus each body of evidence started the GRADE assessment as low certainty.

a. Downgraded by one level for imprecision. The confidence interval for the OR of the combined exposure to NSAIDs and acute respiratory infections overlaps with the confidence interval of the OR for exposure to NSAIDs alone and to acute respiratory infections alone, indicating that the effects of NSAIDs on cardiovascular events in individuals with acute respiratory infections are unclear. Confidence intervals include the possibility of positive, null or negative effects of NSAIDs in individuals with acute respiratory infections. b. Downgraded by one level for imprecision. The confidence interval is wide and includes the possibility of positive, null or negative effects.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n.a.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n.a.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040990.R1
Article Type:	Original research
Date Submitted by the Author:	22-Sep-2020
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Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	General practice / Family practice, Infectious diseases, Pharmacology and therapeutics, Respiratory medicine
Keywords:	Adverse events < THERAPEUTICS, Respiratory infections < THORACIC MEDICINE, CLINICAL PHARMACOLOGY, VIROLOGY

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

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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 utilization, 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 utilization, 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, SARS or MERS; none examined inpatient healthcare utilization, quality of life or long-term survival. Effects of NSAIDs on mortality and cardiovascular events in adults with viral respiratory infections are unclear (3 observational studies; very low certainty). Children with empyema and gastrointestinal bleeding may be more likely to have taken NSAIDs than children without these conditions (2 observational studies; very low certainty). In patients aged 3 years and older with acute respiratory infections, ibuprofen is associated with a higher rate of re-consultations with general practitioners than paracetamol (1 randomized controlled trial (RCT); low certainty). The difference in death from all causes and hospitalization 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 events 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.

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Registration: Registered with PROSPERO (CRD42020176056) and the Open Science Framework (osf.io/snrp4).

Keywords: non-steroidal anti-inflammatory drugs, viral respiratory infections, adverse effects, side effects, COVID-19

Article Summary

Strengths and limitations of this study:

- We conducted a rapid systematic review following Cochrane rapid review guidance and the PRISMA guideline
- We systematically searched three databases and conducted forward- and backward-citation searches
- We followed a pre-specified 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 NSAIDs in patients with bacterial respiratory infections, which have been summarised in existing reviews

Wordcount: 3,454 words

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

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unselective cyclooxygenase (COX) inhibitors (e.g. ibuprofen, aspirin, diclofenac and naproxen) as well as selective COX 2 inhibitors or coxibs (e.g. 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 co-morbidities.[1-3] Well-established adverse effects include gastrointestinal ulcers and bleeding[1] 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 co-morbidities. This includes myocardial infarction,[6] ischemic and hemorrhagic 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 disease (COPD)[12] 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: i) specific adverse events that likely would not occur due to either exposure alone; ii) a worsening of the course of the infection; or iii) an increase in the rate and severity of the known side effects of NSAIDs.

These concerns, notably regarding COVID-19, led the World Health Organization (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

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syndrome, acute organ failure and opportunistic infections), acute healthcare utilization (including hospitalization, 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 (registration number: CRD42020176056) and the Open Science Framework (osf.io/snrp4). Methods are based on Cochrane Rapid Review guidance.[18] Reporting follows the PRISMA guideline.

Search strategy and selection criteria

We searched MEDLINE, EMBASE and the WHO COVID-19 database[19] up to 31 March 2020. We conducted forward- and backward-citation searches in Scopus using references of existing reviews and included studies. Our full search strategy is shown in the supplementary 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 percent 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 utilization, explicit quality of life measures or long-term survival.

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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 (i.e. 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 pre-tested data extraction form (supplementary 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 (EPOC) group for all remaining study designs.[24] We applied 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 (i.e. case-control studies and large RCTs with > 1000 participants)

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as these studies best addressed the commissioned review question. For the remaining studies in children, we mapped the evidence, i.e. 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 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 pre-specified in our protocol. For dichotomous outcomes this includes risk ratios (RRs) and odds ratios (ORs). We extracted and report adjusted results as provided by the included studies. We included 95% confidence intervals (CIs) when these were reported by primary studies.

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 Munich, Germany. The review question was set by 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.

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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 supplementary appendix. Through database and forward- 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, seven cohort studies, three case-crossover studies, three non-randomised controlled trials (NRCTs), one case-control study and one case series. The total number of participants was 172,381 (median: 174, range: 20 to 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, three cohort studies[26-28] and two case-crossover studies[8 9] in adults, and three case-control studies [29 30] and four studies reporting on one RCT in children.[31-34] One retrospective cohort study[27] and one RCT[21] included both adults and children. The latter included participants aged three 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

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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, four cohort studies, four NRCTs and one case series in children. Details on the population, intervention and comparison, outcomes and study designs of included studies are provided in the supplementary appendix.

Findings for adults

Summary of findings for the effects of NSAIDs on mortality and cardiovascular events in adults with viral respiratory infections are shown in Table 3. Effects on the rate of re-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 risk ratio (aRR): 0.9, 95% CI: 0.5-1.6). The confidence interval 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 Table s1 in the supplementary appendix).

Two case-crossover studies in 9,793 patients with myocardial infarction and 29,518 patients with ischemic or hemorrhagic stroke assessed effects on cardiovascular events.[8 9] Both studies report multiple indirect comparisons, comparing adults without acute respiratory infection and not exposed to NSAIDs to: i) adults exposed to both an acute respiratory infections and NSAIDs; ii) adults with an acute respiratory infection but not exposed to NSAIDs; and iii) adults without an acute respiratory infection but exposed to NSAIDs. Both studies report higher odds ratios (ORs) for the combined exposure to NSAIDs and acute respiratory

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infections than for the exposure to either acute respiratory infections or NSAIDs alone (see Table 4). As the confidence intervals 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 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 (coxibs, diclofenac and mefenamic acid). However, confidence intervals overlap, and include the possibility of negative, null or positive effects (very low certainty evidence) (see supplementary appendix, Table s1).

We identified 28 RCTs[21 22 35-60] and two 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 to 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 syncopation[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 re-consultations, presented below.[21]

One RCT in 889 patients aged 3 years or older with a follow-up of four weeks assessed effects on the rate of re-consultations 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 re-consulations for new or unresolved symptoms or complications than paracetamol (acetaminophen)

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(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 are shown in Tables s2 and s3 in the supplementary appendix.

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: 0.7-3.2; 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 (aOR for empyema: 2.8, 95% CI: 1.4-5.6; aOR for gastrointestinal bleeding: 8.2, 95% CI: 2.6-26.0; 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 percentage point 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 assessment of the certainty of evidence for differences between the ibuprofen and the

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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)

Fourty-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 to acetaminophen (paracetamol) is associated with a higher rate of re-consultations with general practitioners.[21]

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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 two weeks, with a number of limitations:

- Searches were limited to three databases, i.e. MEDLINE, EMBASE and the WHO COVID-19 database, complemented with forward- and backward-citation searches. We did not search for or include sources of grey literature or pre-prints, 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 (i.e. case control studies and large RCTs). The decision to exclude other studies in children from evidence synthesis was taken post hoc.

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- 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 (e.g. 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 reviews[63] 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, i.e. NSAID use vs. 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

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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.

Captions:

- Figure 1: PRISMA flow chart
- Figure 2: Risk of bias of case-control and case-crossover studies
- Figure 3: Risk of bias of studies other than case-control and case-crossover studies
- Table 1: Inclusion criteria
- Table 2: Exclusion criteria
- Table 3: Summary of findings for the effects of NSAIDs on mortality and cardiovascular events in adults with viral respiratory infections
- Table 4: Summary of findings for the effects of NSAIDs on the rate of re-consultations with general practitioners in patients with acute respiratory infections

Tables

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Table 1

Table 1: Inclusion criteria		
Population	**Humans of any age with acute viral respiratory infections**, with or without co-morbidities (e.g. 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 etiology 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 and ketoprofen, etc.
		Selective COX 2 inhibitors: Celecoxib, Rofecoxib, Etoricoxib, Lumiracoxib, and Valecoxib, etc.
Comparison	**No or different NSAID**	No NSAID (including other antipyretic and analgesic drugs, e.g. paracetamol/ acetaminophen)
		Different dose or application of NSAID
		Different NSAID (e.g. aspirin versus ibuprofen)
Outcomes	**Acute severe adverse events, acute healthcare utilization and longer-term effects**	**Acute severe adverse events:** ● Mortality ● Acute respiratory distress syndrome (ARDS) ● Acute organ failure (including acute renal failure) ● Cardiovascular events ● Opportunistic infections ● Severe acute allergic and hypersensitivity reactions ● Other, as reported
		Acute healthcare utilization: ● Rate and length of hospitalization ● Rate and length of intensive care unit (ICU) utilization ● Rate and length of supplemental oxygen therapy ● Rate, length and type of mechanical ventilation (invasive vs. non-invasive) ● Other, as reported
		Longer-term effects: ● Explicit quality of life measures ● Long-term survival
Study designs	**Any systematic empirical study design**	Randomized controlled trials
		Cohort studies
		Case-control-studies
		Case series with > 10 patients

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		Case series with < 10 patients (only for COVID-19, SARS and MERS)

Table 2

Table 2: Exclusion criteria	
Population	• Patients with acute bacterial respiratory infections • Patients with non-respiratory viral infections • Patients with hemorrhagic fevers (including Dengue and Ebola) • Patients with infections treated with antibiotics • Patients with pneumonia, unless specified explicitly as being of viral etiology
Intervention / Exposure	• NSAIDs no longer approved or marketed in key markets (e.g. US, Europe) • Non-systemic/topical application of NSAIDs, including lozenges, sprays, and microgranules • Corticosteroids • Paracetamol (acetaminophen)
Outcomes	• 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 cyclooxygenase (COX) 2 inhibitors and diclofenac, as these are well established • Allergic and hypersensitivity reactions occurring in general, i.e. 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 (e.g. pain, nasal congestion)
Study designs	• Non-empirical studies (e.g. commentaries) • Animal studies • Mechanistic data

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Table 3

Table 3. Use of NSAIDs compared to no use of NSAIDs in adults with acute respiratory infections

Patient or population: adults with acute respiratory infections (ARI)
Intervention: use of NSAIDs
Comparison: no use of NSAIDs

Outcomes	Impact	№ of participants (studies)	Certainty of the 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 - 1.6)	683 (1 retrospective, registry-based cohort study)	⊕◯◯◯ VERY LOW [a]
Ischemic stroke Acute respiratory infection Follow-up: exposure in case period (7 days prior to event) was compared to control period (365 days prior to case period)	**Wen 2018** Compared to no use of NSAIDs in adults without ARI (baseline): Risk associated with NSAID use and ARI episode: aOR = 2.27 (95% CI: 2.00- 2.58) Risk associated with ARI episode: aOR = 2.11 (95% CI: 1.91 - 2.34) Risk associated with NSAID use: aOR = 1.38 (95% CI: 1.30 - 1.46)	23618 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
Hemorrhagic stroke Acute respiratory infection Follow-up: exposure in case period (7 days prior to event) was compared to control period (365 days prior to case period)	**Wen 2018** Compared to no use of NSAIDs in adults without ARI (baseline): Risk associated with NSAID use and ARI episode: aOR = 2.28 (95% CI: 1.71-3.02) Risk associated with ARI episode: aOR = 1.63 (95% CI: 1.31-2.03) Risk associated with NSAID use: aOR = 1.49 (95% CI: 1.31-1.69)	(5900 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
Myocardial infarction Acute respiratory infection Follow-up: exposure in case period (7 days prior to event) was compared to control period (365 days prior to case period)	**Wen 2017** Compared to no use of NSAIDs in adults without ARI (baseline): Risk associated with NSAID use and ARI episode: aOR = 3.41 (95% CI: 2.80-4v16) Risk associated with ARI episode: aOR = 2.65 (95% CI: 2.29-3.06) Risk associated with NSAID use: aOR = 1.47 (95% CI: 1.33-1.62)	9793 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]

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

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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

Explanations: a. Downgraded by 1 level for imprecision.

Table 4

Table 4: Use of ibuprofen vs. 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	№ of participants (studies)	Certainty of the evidence (GRADE)
Re-consultation 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: 1.12-2.38)	595 participants (1 RCT)	⨁⨁◯◯ LOW [a,b]

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

Explanations

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

b. Downgraded evidence by 1 level for indirectness: advice to use vs. direct use.

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Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

Funding

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

Author Contributions

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.

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This systematic review was requested by the World Health Organization. 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 World Health Organization.

Acknowledgements

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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 WHO that defined the review question and offered guidance despite the enormous pressures on everyone's time.

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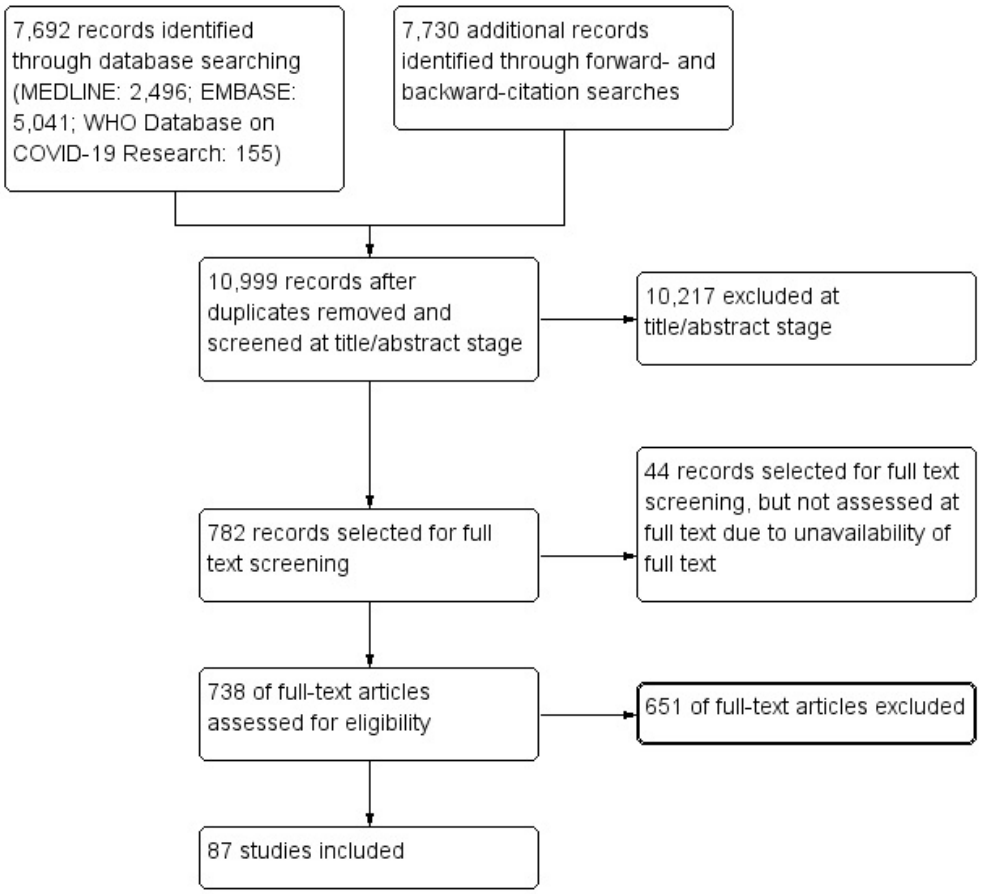

PRISMA flow chart

163x148mm (96 x 96 DPI)

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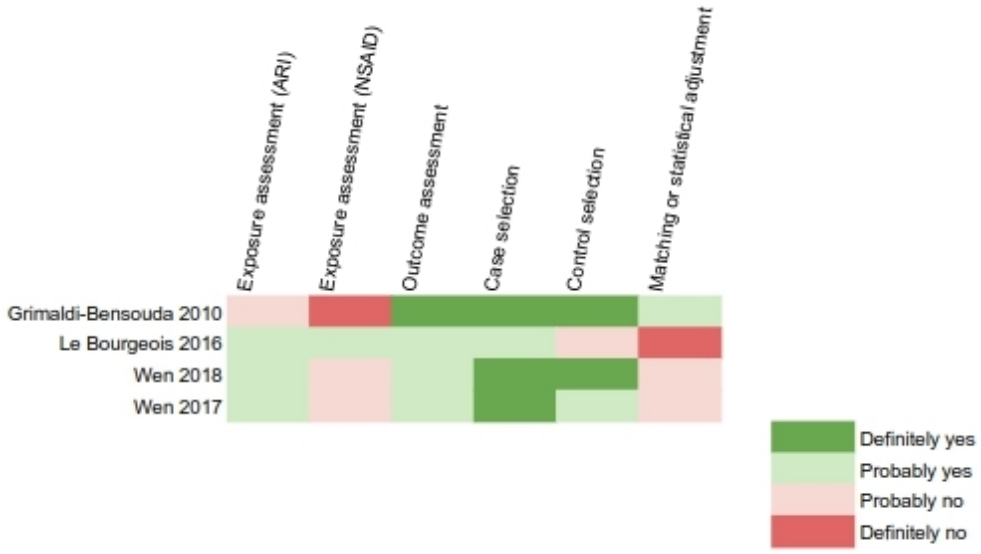

Risk of bias of case-control and case-crossover studies

132x82mm (96 x 96 DPI)

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Risk of bias of studies other than case-control and case-crossover studies

134x172mm (96 x 96 DPI)

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Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with viral respiratory infections: Rapid review

Supplementary appendix

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1. Search strategy for MEDLINE

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)** 1946 to March 19, 2020
Search Strategy:

#	Searches	Results
1	exp Anti-Inflammatory Agents, Non-Steroidal/	195828
2	exp cyclooxygenase Inhibitors/	127691
3	exp cyclooxygenase 2 Inhibitors/	13390
4	nsaid*.mp.	25230
5	((non-steroid* or nonsteroid* or non steroid*) adj2 (anti-inflammator* or antiinflammator* or anti inflammator*)).mp.	86055
6	(aceclofenac or acemetacin or carbasalate calcium or clonixin or dexibuprofen or etoricoxib or flufenamic acid or lornoxicam or loxoprofen or lumiracoxib or lysine acetylsalicylate or mefenamic acid or niflumic acid or parecoxib or rofecoxib or salsalate).mp.	10270
7	(tiaprofenic acid or tolfenamic acid or valdecoxib).mp.	1267
8	apazone.mp.	173
9	aspirin.mp.	66455
10	celecoxib.mp.	6850
11	ibuprofen.mp.	14692
12	diclofenac.mp.	12990
13	diflunisal.mp.	796
14	etodolac.mp.	679
15	fenoprofen.mp.	492
16	flurbiprofen.mp.	2655
17	indometacin.mp.	893
18	indomethacin.mp.	42523
19	ketoprofen.mp.	4277
20	ketorolac.mp.	3118
21	Meclofenamic.mp.	1146
22	meclofenamate.mp.	977
23	meloxicam.mp.	2184
24	meloxicam.mp.	2184
25	nabumetone.mp.	489
26	naproxen.mp.	6844
27	nimesulide.mp.	1703
28	oxaprozin.mp.	162
29	phenylbutazone.mp.	7171
30	piroxicam.mp.	3942
31	sulindac.mp.	2057
32	tenoxicam.mp.	622
33	tolmetin.mp.	1449
34	**or/1-33**	**256116**

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35	exp Coronavirus/	11361
36	exp Coronavirus Infections/	9639
37	(Coronavir* or Corona virus or covid* or Middle East Respiratory Syndrome or MERS or Severe Acute Respiratory Syndrome or SARS or nCov* or HCoV*).mp.	24300
38	exp Severe Acute Respiratory Syndrome/	4460
39	**or/35-38**	**25948**
40	exp Influenza, Human/	48266
41	exp Influenzavirus A/	43175
42	exp Influenzavirus B/	4211
43	(influenza* not h?em?phil* influenza*).ti,ab,kf.	95703
44	(flu or H1N1 orH2N2 or H3N2 or H1N12 or H5N1).ti,ab,kf.	24523
45	**or/40-44**	**111043**
46	exp Common Cold/	4184
47	common cold*.ti,ab,kf.	3955
48	coryza.ti,ab,kf.	643
49	upper respiratory infection*.mp.	2670
50	exp upper respiratory tract infection/	352313
51	viral respiratory tract infection*.mp.	385
52	urti.ti,ab,kf.	855
53	viral respiratory infection.mp.	261
54	(respiratory adj2 virus).mp.	18936
55	(respiratory adj2 viral).mp.	4736
56	Rhinitis/	12478
57	rhinitis.ti,ab,kf.	27388
58	exp Pharyngitis/	15528
59	pharyngitis.ti,ab,kf.	5754
60	RSV.mp.	11711
61	exp Nasopharyngitis/	432
62	nasopharyngitis.ti,ab,kf.	961
63	exp Laryngitis/	3984
64	laryngitis.ti,ab,kf.	2041
65	respiratory syncytial virus.mp.	14116
66	exp respiratory syncytial virus/	8670
67	exp rhinovirus/	3677
68	rhinovirus*.mp.	6170
69	(vir* adj2 pneumonia).ti,ab,kf.	2521
70	exp Pneumonia, Viral/	5512
71	parainfluenza virus 1, human/	2839
72	parainfluenza virus 3, human/	1152
73	**or/46-72**	**404261**
74	(respiratory distress syndrome or ARDS or lung injury).ti,ab,kf.	50457
75	exp Respiratory Distress Syndrome, Adult/	18986
76	**or/74-75**	**55783**

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77	(virus or viral).ti,ab,kf.	818649
78	**76 and 77**	**1683**
79	**39 or 45 or 73 or 78**	**478967**
80	**34 and 79**	**3761**
81	exp animals/ not humans/	4680615
82	**80 not 81**	**3048**
83	(english or german).lg.	26997379
84	**82 and 83**	**2496**

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2. Search strategy for EMBASE

Database(s): **Embase** 1974 to 2020 March 19
Search Strategy:

#	Searches	Results
1	exp nonsteroid antiinflammatory agent/	724205
2	nsaid*.mp.	45078
3	((non-steroid or nonsteroid or non steroid or non steroids) adj2 (antiinflammatory or antiinflammatory or anti inflammator)).mp.	121352
4	apazone.mp.	8
5	(aceclofenac or acemetacin or carbasalate calcium or clonixin or dexibuprofen or etoricoxib or flufenamic acid or lornoxicam or loxoprofen or lumiracoxib or lysine acetylsalicylate or mefenamic acid or niflumic acid or parecoxib or rofecoxib or salsalate or tiaprofenic acid or tolfenamic acid or valdecoxib).mp.	32918
6	azapropazone/	1157
7	aceclofenac/ or acemetacin/ or carbasalate calcium/ or clonixin/ or dexibuprofen/ or etoricoxib/ or flufenamic acid/ or lornoxicam/ or loxoprofen/ or lumiracoxib/ or lysine acetylsalicylate/ or mefenamic acid/ or niflumic acid/ or parecoxib/ or rofecoxib/ or salsalate/ or tiaprofenic acid/ or tolfenamic acid/ or valdecoxib/	31857
8	exp acetylsalicylic acid/	207229
9	aspirin.mp.	116112
10	celecoxib/	21891
11	celecoxib.mp.	22410
12	exp diclofenac/	39567
13	diclofenac.mp.	41365
14	diflunisal/	2736
15	diflunisal.mp.	2824
16	etodolac/	2697
17	etodolac.mp.	2752
18	fenoprofen/	2666
19	fenoprofen.mp.	2885
20	flurbiprofen/	7633
21	flurbiprofen.mp.	8192
22	exp ibuprofen/	49352
23	ibuprofen.mp.	51294
24	indometacin/	77047
25	indomethacin.mp.	41931
26	ketoprofen/	13036
27	ketoprofen.mp.	13592
28	ketorolac/	9703
29	ketorolac.mp.	11659
30	meclofenamic acid/	2804
31	meclofenamate.mp.	1447
32	meloxicam/	7073

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33	meloxicam.mp.	7290
34	nabumetone/ or nabumetone.mp.	2035
35	naproxen/ or naproxen.mp.	26999
36	nimesulide/ or nimesulide.mp.	4832
37	oxaprozin/ or oxaprozin.mp.	750
38	phenylbutazone/ or phenylbutazone.mp.	12841
39	piroxicam/ or piroxicam.mp.	11676
40	sulindac/ or sulindac.mp.	7587
41	tenoxicam/ or tenoxicam.mp.	2102
42	tolmetin/ or tolmetin.mp.	2688
43	**or/1-42**	**746194**
44	coronaviridae/	890
45	coronavirinae/	1047
46	exp coronavirus infection/	11075
47	coronavir*.mp.	18736
48	ncov*.mp.	310
49	covid*.mp.	6588
50	middle east respiratory syndrome.mp.	2678
51	mers.mp.	4610
52	severe acute respiratory syndrome.mp.	9798
53	sars.mp.	10912
54	HCoV*.mp.	690
55	**or/44-54**	**35940**
56	(respiratory distress syndrome or ARDS or lung injury).ti,ab.	71093
57	exp adult respiratory distress syndrome/ or exp acute lung injury/	46394
58	**or/56-57**	**84601**
59	(virus or viral).ti,ab.	926277
60	**58 and 59**	**3110**
61	exp influenza/	83750
62	(influenza* not (h?em?phil* influenza* or "h influenza*")).mp.	137610
63	flu.ab,ti.	19582
64	(h1n1 or h5n1 or h3n2).mp.	39113
65	**or/61-64**	**147898**
66	exp common cold/	8004
67	common cold*.ti,ab.	4466
68	coryza.ti,ab.	586
69	upper respiratory infection*.ti,ab.	3956
70	upper respiratory tract infection/	27635
71	urti.ti,ab.	1372
72	rhinit*.ti,ab.	39318
73	rhinitis/	18800
74	pharyngitis/	15196
75	pharyngit*.ti,ab.	7144

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76	rhinopharyngitis/	12432
77	laryngitis/	3672
78	laryngit*.ti,ab.	1987
79	nasopharyngit*.ti,ab.	2472
80	**or/66-79**	**109716**
81	(virus or viral).mp.	1487387
82	**80 and 81**	**13487**
83	rhinovirus.ti,ab.	6844
84	exp rhinovirus/	8285
85	vir* pneumonia.ab,ti.	1760
86	exp virus pneumonia/	14441
87	exp viral respiratory tract infection/	3869
88	exp parainfluenza virus infection/	1261
89	exp Human respiratory syncytial virus/	4427
90	respiratory syncytial virus.mp.	19005
91	**or/83-90**	**42933**
92	**55 or 60 or 65 or 82 or 91**	**213662**
93	**43 and 92**	**6543**
94	animal/ not human/	1061398
95	**93 not 94**	**6525**
96	(english or german).lg.	29902747
97	**95 and 96**	**6214**
98	**limit 97 to (article or article in press or erratum or letter or note or "review" or short survey)**	**5041**

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3. Search strategy for the WHO COVID-19 Research Database

We searched titles and abstracts with the following combination of search terms: “nsaids or nsaid or steroid or steroidal or nonsteroid or nonsteroidal anti-inflammatory or antiinflammatory or cyclooxigenase or aceclofenac or acemetacin or carbasalate calcium or clonixin or dexibuprofen or etoricoxib or flufenamic or lornoxicam or loxoprofen or lumiracoxib or acetylsalicylate or mefenamic or niflumic or parecoxib or rofecoxib or salsalate or tiaprofenic or tolfenamic or valdecoxib or apazone or aspirin or celecoxib or ibuprofen or diclofenac or diflunisal or etodolac or fenoprofen or flurbiprofen or indometacin or indomethacin or ketoprofen or ketorolac or Meclofenamic or meclofenamate or meloxicam or meloxicam or nabumetone or naproxen or nimesulide or oxaprozin or phenylbutazone or piroxicam or sulindac or tenoxicam or tolmetin or adverse or side effect or side effects or iatrogenic or harm or harmful or safe or safety”

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References used for the third round of forward- and backward-citation searches

For the third round of forward- and backward-citation searches we used the references of all studies included based on the database searches and the first and second rounds of forward- and backward-citation searches (n=73), as well as the references of the following reviews:

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5. Data extraction form

Items of the data extraction form for studies in adults:

Study information:

- Reviewer initials
- Study ID
- Study title
- Publication year
- Study design
- Study length

Inclusion criteria:

- Study in humans?
- Empirical data?
- Study size?
- NSAID exposure?
- Viral respiratory infection?
- Relevant outcome?
- Link between NSAID, viral infection, and outcome?
- Comments

Population:

- Short verbal description of the population
- Total number of participants
- Disease/pathogen class
- Disease(s)
- Pathogen(s)
- Share of participants with a viral respiratory infection
- Severity of disease
- ARDS
- Underlying or pre-existing conditions, co-morbidities
- Age group
- Mean age
- Sex
- Ethnicity
- Country
- Comments

Intervention and comparison:

- Drug(s)
- Application
- Dosage and length of application
- Reason for the use or administration of NSAID
- Prescription vs. Over-the-counter (OTC) use
- NSAID used prior to or initiated during the viral respiratory infection
- Comparison
- Comments

Risk of bias assessment:

- Random sequence generation
- Allocation concealment
- Similarity of baseline outcome measures
- Similarity of baseline characteristics
- Incomplete outcome data
- Blinding
- Contamination
- Selective reporting
- Other risks of bias

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Outcomes (general):

- Severe acute adverse events?
- Healthcare utilization?
- Quality of life?
- Quote of all information on adverse outcomes reported in the study
- Type of AO reporting
- Details on how AO were assessed

Outcome (for specific outcome measures):

- Type of outcome
- Verbal summary of the outcome
- Verbal summary of the link between NSAID, viral infection, and outcome
- Follow-up
- Effect measure
- Total number of participants
- Outcome in the IG
- Participants in IG
- Outcome in the CG
- Participants in CG
- Summary RoB
- Comments

Items of the data extraction form for studies in children:

- Study ID
- Study title
- Study design
- Nr of participants
- Length of follow up
- Drugs used
- Disease / condition / pathogen
- Outcome measures

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6. Search log

Initial search	
Source	Nr. of hits
MEDLINE	2496
EMBASE	5041
First round of backward-citation search	1849
First round of forward-citation search	1183
Sum before de-duplication	10569
Sum after de-duplication	9047
Second round of backward- and forward-citation searches	
Second round of backward-citation search	359
Second round of forward-citation search	400
Sum before de-duplication	759
Sum after de-duplication	289
Third round of backward- and forward-citation searches	
Third round of backward-citation search	1319
Third round of forward-citation search	2620
Sum before de-duplication	3939
Sum after de-duplication	1508
WHO Database on Covid-19 research	
Initial search (March 25, 2020)	155
Excluded at title/abstract screening stage	148
Included for full text screening (this includes three studies in Chinese which we were unable to assess at full text)	7
Summary	
Total number of titles/abstracts screened (MEDLINE, EMBASE, Scopus, WHO Covid-19 database)	10999
Excluded at title/abstract screening stage	10196
Included at title/abstract screening stage and assessed at full text	738
Included at title/abstract screening stage, but not assessed at full text due to unavailability of full text	65
Excluded at full text screening stage	654
Included studies	84

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7. Potentially relevant studies for which no full text could be obtained

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9. Characteristics of studies included in the evidence synthesis

Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
Azuma 2010	Japan	N: 170 adults Age range: 20-70 years Mean age: n.r. Disease: Upper respiratory tract infection (URTI)	Zaltoprofen, Placebo	Pain and fever relief	Dosage: Zaltoprofren 1: 160mg Zaltoprofren 2: 80mg Application: oral Frequency: once	RCT	6 hours	Counts of Adverse Effects (AEs): Symptoms after administration of study medication
Azuma 2011	Japan	N: 330 adults Mean age: Zaltoprofen: 33 years Loxoprofen: 36 Placebo: 36 Age range: 20-70 years Disease: Febrile URTI	Zaltoprofen, Loxoprofen, Placebo	Pain and fever relief	Dosage: Zaltoprofen: 160 mg Loxoprofen: 60mg Application: oral Frequency: once	RCT	4 hours	Counts of AEs: Symptoms after administration of study medication
Bachert 2005	Russia	N: 392 adults Age range: 18 - 65 years Mean age: 37.4 years Disease: Febrile URTI	Aspirin, Acetaminophen, Placebo	Pain and fever relief	Dosage: Aspirin 1: 500mg Aspirin 2: 1000mg Acetaminophen 1: 500mg Acetaminophen 2: 1000mg Application: oral Frequency: once	RCT	6 hours	Counts of (severe) AEs
Bettini 1986	Italy	N: 120 adults Age range: n.r. Mean age: 37 years Disease: Influenza-related fever	Diclofenac, Aspirin	Fever relief	Dosage: 1) Diclofenac 25 mg 2) Aspirin 500 mg Application: oral Frequency: 1) every 12 hours for two days 2) every 8 hours for two days	RCT	2 days	Count of AEs: Medication side effects
Boureau	France	N: 113 adults	Ibuprofen,	Symptom	Dosage: Ibuprofen: 400mg	RCT	48 hours	Counts of AEs:

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Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
1999		Age range: 18-60 years Mean age: n.r. Disease: Tonsillitis	Paracetamol	relief	Paracetamol: 1000mg Application: oral Frequency: once			symptoms after administration of study medication
Broggini 1986	Italy	N: 30 adults Age range: n.r. Mean age: Flurbiprofen 34.4 years; Aspirin 41.6 years Disease: Influenza	Flurbiprofen, aspirin	Symptom relief	Dosage: 1) Flurbiprofen 2) aspirin Application: oral Frequency: twice daily over four days	RCT	4 days	Count of AEs: Medication side effects
Ebel 1985	USA	N: 312 adults Age range: 18 - 70 years Mean age: male: 38.5 years female 43.5 Disease: URTI	Sulindac, Placebo	Symptom relief	Dosage: Sulindac 200mg Application: n.r. Frequency: twice per day, 7 days	RCT	7 days	Counts of (severe) AEs
Eccles 2003	Sweden, UK	N: 279 adults Age range: 18-60 years Mean age: IG 25.5 years CG 24.5 years Disease: URTI	Acetylsalicylic Acid, Placebo	Symptom relief	Dosage: 400mg ASA Application: oral Frequency: 1-2 tablets every 4-6 hours for 3 days	RCT	3 days	Counts of AEs: Medication side effects
Eccles 2013	UK	N: 833 participants Age range: n.r. Mean age: n.r. Disease: URTI	Aspirin + Pseudoephedrine, Aspirin, Pseudoephedrine, Placebo	Symptom relief	Dosage: 1) 500 mg ASA + 30 mg PSE 2) 500 mg ASA 3) 60 mg PSE Application: oral Frequency: 2-3 doses on day 1, 3 doses for another 3 days	RCT	7 days	Counts of AEs
Epperly 2016	USA	N: 683 adults 838 children;	NSAIDs, Aspirin,	Improvement of the	Dosage: n.r. Application: most likely oral intake	Retrospective regi	Adults: 60 days	Risk of mortality

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Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
		Age range: n.r. Mean age: Adult NSAID user: 42.0 years; Adult non-user: 45.6 Adult aspirin user: 51.2 years Adult non-user: 44.1 Child NSAID user: 7.9 years non-user: 7.1 Disease: pH1N1	non-use	medical course of influenza	Frequency: n.r.	stry-based cohort study	Children: 90 days	
Gehanno 2003	France	N: 343 Age range: 20-60 years Mean age: 40 years Disease: Febrile sore throat	Diclofenac potassium, Paracetamol	Pain and fever relief	Dosage: Diclofenac potassium 6.25 mg, 12.5 mg and 25 mg Paracetamol: 1000 mg Application: Oral Frequency: Once	RCT	10 days	Counts of AEs
Goto 2007	Japan	N: 189 Age group: 18-65 years Mean age: Loxoprofen: 29.3 years, Placebo 27.6 years Disease: URTI-like symptoms of the nose and pharynx	Loxoprofen, Placebo	Symptom relief	Dosage: Loxoprofen 60 mg Application: oral Frequency: 2-3 times a day for at most 7 days	RCT	7 days	Counts of AEs
Graham 1990	Australia	N: 60 adults Age range: 18 - 30 years Mean age: n.r. Disease: URTI	Aspirin, Acetaminophen, Ibuprofen	Symptom relief	Dosage: Aspirin: 500mg Acetaminophen: 500mg Ibuprofen: 200mg Application: Oral Frequency: Daily for 7 days Aspirin: 4 doses Acetaminophen: 4 doses Ibuprofen: 3 doses	RCT	28 days	Counts of AEs: Symptoms after administration of study medication
Grebe	Germany	N: 356 adults	Diclofenac-K,	Symptom	Dosage: Diclofenac-K: 12.5mg,	RCT	3 days	Counts of AEs

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Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
2003		Age range: ≥ 18 years Mean age: 40.2 years Disease: Influenza-like symptoms	Ibuprofen, Placebo	relief	multiple, flexible dosing regimen Ibuprofen: 200mg tablets multiple, flexible dosing regimen Application: oral Frequency: 3 days			
Grimaldi-Bensouda 2010	France	N: 177 children Age range: 2 months - 16 years Mean age: n.r. Disease: Fever, pain, rheumatic indication	Ibuprofen, Aspirin, non-use	Relief of fever	Dosage: Ibuprofen: 18 mg/kg Aspirin: 24 mg/kg Fenamates: 32m g/kg Ketoprofen: 2 mg/kg Flurbiprofen: 2 mg/kg Naproxen: 11.5 mg/kg Application: most likely oral Frequency: Daily, Mean duration of use: 1.9±1.5 days	Case-cross-over study	7 days	Risk of upper gastrointestinal bleeding
Grunthal 2008	Germany	N: 2341 Age range: n.r. Mean age: ca. 40 years Disease: Cold	acetylsalicylate (aspirin) + pseudoephedrin, paracetamol + caffeine + chlorphenamine maleat+ vitamin C	Symptom relief	Dosage: 1) acetylsalicylate (aspirin) (500mg) + pseudoephedrin (30mg) 2) paracetamol (200mg) + caffein (25mg) 3) chlorphenamin maleat (2,5 mg) + vitamin C (150 mg) Application: oral Frequency: 1) mean: 1.6 doses 2) mean: 1.9 doses	Cohort study	3 days	Counts of AEs
Hung 2017	Hong Kong	N: 217 adults Age range: ≥ 18 years Median: 80 years Disease: Influenza A (H3N3)	Clarithromycin + Naproxen + Oseltamivir, Oseltamivir	Treatment of severe influenza	Dosage: 1) triple combination (Clarithromycin 500 mg + Naproxen 200 mg + Oseltamivir 75 mg) 2) Oseltamivir 75 mg Application: oral	RCT	30 days	Risk for Mortality (at 30 / 90 days), duration of hospitalization

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Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
					Frequency: Group 1: 1) twice daily for two days and 2) twice daily for three days Group 2: 2) twice daily for five days			
Le Bourgeois 2016	USA	N: 166 children Age range: 3 -15 years Mean age: Cases: 4.1 ± 2.3 Controls: 3.8 ± 2.3 Disease: Acute viral infection (upper respiratory tract viral infections, lower respiratory tract viral infections and others)	Ibuprofen, Ketoprofen, non-use	Relief of symptoms	Dosage: n.r. Application: n.r. Frequency: 1, 2 and 3 consecutive days intake of Ibuprofen or Ketoprofen	Matched case-control study	Cases and controls: 15 days (retrospective)	Risk of hospitalization (empyema)
Lesko 1995	USA	N: 83,915 children Age range: 6 months - 12 years Mean age: n.r. Disease: Febrile illness	Ibuprofen, Paracetamol	Relief of symptoms of febrile illness	Dosage: Ibuprofen 1: 5mg/kg Ibuprofen 2: 10mg/kg Paracetamol: 10 mg/kg Application: oral Frequency: Ibuprofen 1 and 2: median number of doses 6-10, median duration 3 days	Randomized Controlled Trial (RCT)	4 weeks	Risk of hospitalization for acute gastrointestinal bleeding, acute renal failure, anaphylaxis or Reye's syndrome Counts of other (severe) AEs leading to hospitalization
Lesko	USA	N: 288 children	Ibuprofen,	Relief of	Dosage: Ibuprofen 1: 5mg/kg	RCT	4 weeks	Risk of renal

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Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
1997		Age range: 6 months - 12 years Mean age: n.r. Disease: Febrile illness	Acetaminophen	symptoms of febrile illness	Ibuprofen 2: 10mg/kg Acetaminophen: 12mg/kg Application: oral Frequency: All: median number of doses 7, median duration 2 days			impairment
Lesko 1999	USA	N: 27,065 children Age range: 1 - 23 months Mean age: n.r. Disease: Febrile illness	Ibuprofen, Acetaminophen	Relief of symptoms of febrile illness	Dosage: Ibuprofen 1: 5mg/kg Ibuprofen 2: 10mg/kg Acetaminophen: 12mg/kg Application: oral Frequency: All: median number of doses 6-10, median duration 3 days	RCT	4 weeks	Risk of hospitalization for acute gastrointestinal bleeding, acute renal failure, anaphylaxis or Reye's syndrome Counts of other (severe) AEs leading to hospitalization
Lesko 2002	USA	N: 1879 children Age range: 6 months - 12 years Mean age: n.r. Disease: Febrile illness	Ibuprofen, Acetaminophen	Relief of symptoms of febrile illness	Dosage: Ibuprofen 1: 5mg/kg Ibuprofen 2: 10mg/kg Acetaminophen: 12mg/kg Application: Oral Frequency: n.r.	RCT	4 weeks	Risk of outpatient visits or hospitalization for asthma
Little 2013	UK	N: 89 children and adults Age range: ≥ 3 years Mean age: Ibuprofen 34; Paracetamol 34; Both 33	Ibuprofen, Paracetamol, Ibuprofen + Paracetamol	Symptom relief	Dosage: n.r. Application: Oral Frequency: Dependent on trial arm; Regular dosing: 4x daily; As required dosing: as required by	RCT	28 days	Healthcare utilization: return visit with new or worsening symptoms or

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Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
		Disease: Respiratory infections (upper and lower)			symptoms up to 4x daily			complicationsof intervention
Llor 2013	Spain	N: 416 Age range: 18-70 years Mean age: 45.1 years Disease: RTI	Ibuprofen, Amoxicillin-clavulanic acid, Placebo	Symptom relief	Dosage: Ibuprofen: 600 mg Amoxicillin-clavulanic acid: 500 mg Application: n.r. Frequency: 3 daily for 10 days	RCT	11-13 days	Counts of AEs: events possible related to drug
Loose 2011	Germany	N: 640 adults Age range: not reported Mean age: 19.6 years Disease: URTI leading to nasal congestion	Aspirin + Pseudoephedrine, Paracetamol + Pseudoephedrine, Placebo	Symptom relief	Dosage:a) ASA + 60mg PSE b) ASA + 30mg PSE c) Paracetamol 1000 mg +60mg PSE d) Placebo Application: oral Frequency: once	RCT	6 h	Counts of AEs
Milvio 1984	Switzerland	N: 50 adults Age range: n.r. Mean age: Nimesulide: 38 years; Benzydamine: 49 years Disease: Inflammation of the ear, nose and throat	Nimesulide, Benzydamine	Treatment of fever and inflammation	Dosage:1) Nimsulide 100 mg 2) Benzydamine 75 mg Application: oral Frequency: twice a day for 10 days	RCT	10 days	Count of AEs: Medication side effects
Nouri 1993	Austria or Switzerland	N: 65 adults Age range: 35-62 years Mean age: IG: 39 years CG: 53 years Disease: Non-bacterial inflammation of the ear, nose and throat	Nimesulide, Naproxen	Treatment of inflammation	Dosage: 1) Nimseluide 100 mg 2) Naproxen 500 mg Application: oral Frequency: Twice daily, mean duration 8.7 days	RCT	10 days	Counts of AEs

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Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
Ottaviani 1993	Italy	N: 940 children and adults Age range: 15-77 years Mean age: 38 years Disease: URTI or Otitis media	Nimesulide	Symptom relief	Dosage: Nimesulide 100 mg Application: oral Frequency: twice a day for or a mean (± SD) of 10 (± 4) days	Cohort study	10 days	Counts of AEs
Schachtel 1988	USA	N: 120 adults Age range: 18 - 88 years Mean age: Ibuprofen: 41.5 years, Acetaminophen: 46.1 Disease: Severe throat pain	Ibuprofen, Acetaminophen, Placebo	Symptom relief	Dosage: Ibuprofen: 400mg Acetaminophen: 1000mg Application: oral Frequency: Once	RCT	1 day	Counts of AEs
Schachtel 1991	USA	N: 210 adults Age range: 18 - 83 years Mean age: 30 Disease: Tonsillopharyngitis/URTI	Aspirin + caffeine, Aspirin, Placebo	Pain relief	Dosage: Aspirin 1: 800mg + 64mg Aspirin 2: 800mg Placebo Application: oral Frequency: Once	RCT	2 hours	Counts of AEs
Schachtel 2007	USA	N: 197 adults Age range: ≥ 18 years Mean age: n.r. Disease: Tonsillopharyngitis	Valdecoxib, Placebo	Symptom relief	Dosage: Valdecoxib 1: 40 mg Valdecoxib 2: 20 mg Placebo Application: n.r. Frequency: once	RCT	24 hours	Counts of AEs
Schachtel 2011	USA	N: 269 adults Age range: 18 - 30 Mean age: 19 Disease: Sore throat	Celecoxib, Placebo	Pain relief	Dosage: Celecoxib 1: 50-mg + 50 mg after 6-12 hours Celecoxib 2: 100-mg + placebo after 6-12 hours Celecoxib 3: 100-mg + 50 mg after 6-12 hours Placebo: placebo + placebo after	RCT	24 hours	Counts of AEs

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Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
					6-12 hours Application: oral Frequency: once			
Smith 2014	USA	N: 207 adults Age range: 18 - 34 years Mean age: 21 years Disease: URTI	Ibuprofen + Caffeine, Ibuprofen, Caffeine, Placebo	Symptom relief	Dosage: Ibuprofen + Caffeine: 200mg + 100mg Ibuprofen: 200mg Caffeine: 100mg Placebo Application: Oral Frequency: once	RCT	3 hours	Counts of AEs
Sperber 1989	USA	N: 58 adults Age range: n.r. Mean age: 20-21 years Disease: Cold	Ibuprofen + Pseudoephedrine, Pseudoephedrine Placebo	Symptom relief	Dosage: Pseudoephidrine + Ibuprofen: 60mg + 200mg Pseudoephidrine 60mg Placebo Application: Oral Frequency: 2 doses the first day, 4 doses over next 4 days	RCT	14 days	Counts of AEs: symptoms after administration of study medication
Sperber 1992	USA	N: 87 adults Age range: n.r Mean age: 21.4 years Disease: Cold	Naproxen, Placebo	Symptom relief	Dosage: See below Application: oral Frequency: Naproxen 1: 1 loading dose (400mg) + 3 times daily 200mg for 5 days Naproxen 2 and 3: 1 loading dose (500mg) + 3 times daily 500mg for 5 days	RCT	5 days	Counts of AEs
Wen 2017	Taiwan	N: 9,793 adults Age range: >20 years	NSAID, No NSAID	Pain and fever relief	Dosage: n.r. Application: n.r.	Case-Crossove	Cases: 7 days	Risk of myocardial infarction

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Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
		Mean age: 72.3 years at diagnosis Disease: Acute respiratory infection (ARI			Frequency: n.r.	r Study		
Wen 2018	Taiwan	N: 29,518 adults Age range: > 20 years Mean age: 73.4 years Disease: Acute respiratory infection (ARI)	NSAID (any single-active-ingredient NSAIDs, non-use	Pain and fever relief	Dosage: n.r. Application: n.r. Frequency: n.r.	Case-Crossove r Study	Cases: 7 days	Risk for ischemic and hemorrhagic stroke
Weckx 2002	Brazil, Colombia and Mexico	N: 357 adults Age range: ≥ 18 years Mean age: Celecoxib once daily: 32 Celecoxib twice daily: 31 Diclofenac: 32 Disease: Viral pharyngitis	Celecoxib, Diclofenac	Symptom relief	Dosage: 1) Celecoxib 200 mg 2) Diclofenac 75 mg Application: oral Frequency: a) 1) once daily b) 1) twice daily, c) 2) twice daily for five days	RCT	5 days	Counts of (serious) AEs
Younkin 1983	USA	N: 47 children and adults Age range: 17-20 years Mean age: n.r. Disease: Influenza	Aspirin, Amantadine		Dosage: Aspirin: 325 mg Amantadine 1: 100mg Amantadine 2: 100mg Application: Oral Frequency: For 5 days Aspirin: 10 daily Amantadine 1: 1 daily Amantadine 2: 1 daily	RCT	7 days	Count of AEs: Medication side effects

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10. Effects on primary outcomes reported by studies included in the evidence synthesis

Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
Comparison of NSAID use with no NSAID use: Effects on mortality				
Epperly 2016	NSAIDs use vs. non-use	Risk for mortality	NSAID use: Risk: 22.7% Non-use: Risk: 24.2% aRR = 0.9 (0.5-1.6)	Effects on mortality of NSAID in adults with H1N1 influenza are unclear. The confidence interval of the effect estimate is large, and includes the possibility of a positive, null or negative effect.
Epperly 2016 (subgroup analyses)	Aspirin use vs. non-use	Risk for mortality	Aspirin use: Risk: 23.8% Non-use: Risk: 24.1% aRR = 1.1 (0.6-1.9)	Effects on mortality of aspirin in adults with H1N1 influenza are unclear. The confidence interval of the effect estimate is large, and includes the possibility of a positive, null or negative effect.
NSAID use vs. no NSAID use: Effects cardiovascular events				
Wen 2017	NSAIDs vs. non-use	Risk for myocardial infarction	NSAID during ARI: aOR = 3.41; (2.80-4.16) ARI without NSAID: aOR = 2.65; (2.29-3.06) NSAID use only: aOR = 1.47 (1.33-1.62) No exposure (reference): aOR = 1	NSAID use in individuals with an acute respiratory infection (ARI) was associated with a higher odds ratio for myocardial infarction compared to: a) individuals with an ARI not exposed to NSAIDs, b) individuals without an ARI exposed to NSAIDs, c) individuals without an ARI not exposed to NSAIDs. Confidence intervals overlap, indicating that the effect of NSAID in patients with ARI on risk for myocardial infarction is unclear. The confidence intervals include the possibility of a positive, null or negative effect.
Wen 2018	NSAIDs vs. non-use	Risk for ischemic stroke	NSAID use during ARI: aOR = 2.27; (2.00-2.58) ARI without NSAID use: aOR = 2.11; (1.91-2.34) NSAID use only: aOR = 1.38 (1.30-1.46) No exposure (reference): aOR	NSAID use in individuals with an acute respiratory infection (ARI) was associated with a higher odds ratio for ischemic stroke compared to: a) individuals with an ARI not exposed to NSAIDs, b) individuals without an ARI exposed to NSAIDs, c) individuals without an ARI not exposed to NSAIDs. Confidence intervals overlap, indicating that the effect of NSAID in patients with ARI on risk for ischemic stroke is unclear. The confidence intervals include the

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Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
			= 1	possibility of a positive, null or negative effect.
Wen 2018	NSAIDs vs. non-use	Risk for hemorrhagic stroke	NSAID during ARI: aOR = 2.28; (1.71-3.02) ARI without NSAID: aOR = 1.63; (1.31-2.03) NSAID use only: aOR = 1.49 (1.31-1.69) No exposure (reference): aOR = 1	NSAID use in individuals with an acute respiratory infection (ARI) was associated with a higher odds ratio for hemorrhagic stroke compared to: a) individuals with an ARI not exposed to NSAIDs, b) individuals without an ARI exposed to NSAIDs, c) individuals without an ARI not exposed to NSAIDs. Confidence intervals overlap, indicating that the effect of NSAID in patients with ARI on risk for hemorrhagic stroke is unclear. The confidence intervals include the possibility of a positive, null or negative effect.
Multiple comparisons: Effects on adverse event counts				
Azuma 2010	Zaltoprofen vs zaltoprofen vs placebo	Counts of severe adverse events (SAEs)	Not explicitly reported	That study reports several mild adverse events, and explicitly states that no severe adverse events occured (Quote: "Three headaches, 2 odynophagias and 2 joint pain cases occurred in the 80-mg group. One odynophagia, 1 joint pain, 1 muscle pain, 1 glutamic oxaloacetic transaminase (GOT) increase and 1 lactate dehydrogenase (LDH) increase occurred in the 160-mg group. All of these events were mild.")
Azuma 2011	Zaltoprofen vs loxoprofen vs placebo	Counts of SAEs	Not explicitly reported	That study reports with regard to observed adverse events that "[t]hese were mostly mild symptoms, and no unknown adverse events were encountered." Moreover, the study reports that "[n]o significant differences existed in the incidence of adverse events among groups." (Full quote: "In the present study, adverse events were seen in 8 of 131 patients (6.1%) in the zaltoprofen group, in 4 of 131 patients (3.1%) in the loxoprofen group, and in 9 of 60 patients (15.0%) in the placebo group. (…) These were mostly mild symptoms, and no unknown adverse events were encountered. In the zaltoprofen group, cases included 1 patient (0.8%) with tonsillitis aggravation, 1 patient (0.8%) with orthostatic hypotension, 1 patient (0.8%) with asthmatic attack, and 2 patients (1.5%) with exanthema/itch sensation. In the loxoprofen group, they included 1 patient (0.8%) with joint pain, 1 patient (0.8%) with urinary protein, and 1 patient (0.8%)

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Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
				with hives.")
Bachert 2005	Aspirin vs acetaminophen (paracetamol) vs placebo	Counts of SAEs	Aspirin: 0 SAEs Acetaminophen: 0 SAEs Placebo: 0 SAEs	The study reports that "[n]o serious or severe adverse events were reported."
Bettini 1986	Diclofenac sodium vs aspirin	Counts of SAEs	Not explicitly reported	The study reports that ["a]s regards side effects, episodes of slight epigastric pain were recorded in one patient treated with Novapirina and in five patients treated with Aspirin. No patient had to discontinue the treatment because of side effects."
Boureau 1999	Ibuprofen vs Paracetamol	Counts of SAEs	Not explicitly reported	The study reports that "[t]here were no serious adverse effects and no statistically significant difference in the incidence of adverse events in the two treatment groups", but provides only very little detail on whether and how SAEs were monitored or reported.
Broggini 1986	Flurbiprofen vs aspirin	Counts of SAEs	Not explicitly reported	The study reports that "[s]ide effects were reported by two cases on ASA (1 dyspepsia necessitating withdrawal of treatment and 1 bitter taste) and 3 cases on flurbiprofen (1 heartburn, 1 drowsiness and 1 nausea)."
Ebel 1985	Sulindac vs placebo	Counts of SAEs	Sulindac: 0 SAEs Placebo: 0 SAEs	The study reports that "[n]one of the adverse experiences reported was rated serious."
Eccles 2003	Aspirin + pseudo-ephedrine vs aspirin; Aspirin + pseudo-ephedrine vs pseudoephedrine; Aspirin + Pseudo-ephedrine vs placebo	Counts of SAEs	Aspirin + pseudoephedrine: 0 SAEs Aspirin: 0 SAEs Pseudoephedrine: 0 SAEs Placebo: 0 SAEs	The study reports that "[n]o serious adverse events were reported."

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Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
Eccles 2013	Aspirin + pseudo-ephedrine vs aspirin; Aspirin + pseudo-ephedrine vs pseudoephedrine; Aspirin + Pseudo-ephedrine vs placebo	Counts of SAEs	Aspirin + pseudoephedrine: 1 SAE Aspirin: 0 SAEs Pseudoephedrine: 0 SAEs Placebo: 0 SAEs	Study reports that "[o]verall one serious adverse event (SAE) occurred. The patient was treated with aspirin plus PSE [pseudoephedrine]. The SAE was a fall, and feeling faint after the fall." The study also notes that "[t]he investigator considered that the fall and the faint feeling were not related to the study drug."
Gehanno 2003	Diclofenac potassium vs Paracetamol	Counts of SAEs	Diclofenac potassium 6.25 mg: 0 SAEs Diclofenac potassium 12.5mg: 0 SAEs Diclofenac potassium 25 mg: 0 SAEs Paracteamol: 0 SAEs	The study reports that the patients reporting any AEs did not differ significantly between study groups. Additionally, they report that "[n]o patients had to be withdrawn from the study because of an adverse experience. There were no serious adverse experiences and no deaths during the trial."
Goto 2007	Loxoprofen vs placebo	Counts of SAEs	Not explicitly reported	The study reports that "[e]ight patients in the loxoprofen group (9.5%) complained of several kinds of adverse events including drowsiness (in three) and thirst (in two) during the follow-up period, which was higher than the one patient in the placebo group (1.1%) with drowsiness."
Graham 1990	Aspirin vs acetaminophen (paracetamol) vs ibuprofen vs placebo	Counts of SAEs	Not explicitly reported	The study does not report explicitly on SAEs, but reports that "the aspirin group experienced more side effects than the other groups. Five in the aspirin group did not complete the full course of medication, because of tinnitus in all 5 cases and gastrointestinal symptoms in 1 of those; they stopped on days 3 and 4. Despite stopping medication, these volunteers continued to participate and completed all other aspects of the study."
Grebe 2003	Diclofenac-K vs ibuprofen vs placebo	Counts of SAEs	Diclofenac-K: 0 SAEs Ibuprofen: 0 SAEs Placebo: 0 SAEs	The study reports that "no serious treatment-related adverse events were reported."

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Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
Grunthal 2008	Acetylsalicylate (aspirin) + pseudoephedrin vs paracetamol + caffeine + chlorphenamine + vitamin C	Counts of SAEs	Not explicitly reported	The study reports that 4.8% of participants receiving paracetamol and 9.8% of participants receiving aspirin reported side effects, which were "mostly of mild or moderate severity". The most common side effects in the aspirin group were "gastric pain, upper abdominal pain and nausea".
Hung 2017	Clarithromycin + naproxen + oseltamivir vs oseltamivir	Counts of SAEs	Not explicitly reported	The study notes that "no patient in our study reported adverse events due to drug-drug interaction." The study does not report explicitly whether and how SAEs were monitored or reported.
Llor 2013	Ibuprofen vs Amoxicillin-clavulanic acid vs Placebo	Counts of SAEs	Ibuoprofen: 0 SAEs amoxicillin-clavulanic acid: 1 SAE Placebo: 0 SAEs	The study reports that AEs were more common in the Aamoxicillin-clavulanic acid group than in the Ibuprofen or placebo groups. The only SAE in recorded in the study, a digestive haemmorrhage requiring admission to the intensive care unit, occurred in the amoxicillin-clavulanic acid group.
Loose 2004	Aspirin + pseudoephedrinevs aspirin + pseudoephedrine + placebo vs acetaminophen (paracetamol) + pseudoephedrine + placebo vs placebo	Counts of SAEs	Aspirin + pseudoephedrine: 0 SAEs Aspirin + pseudoephedrine + placebo: 0 SAEs Paracetamol + pseudoephedrine + placebo: 0 SAEs Placebo: 0 SAEs	The study reports that "[d]uring the study, 153 adverse events (AEs) in 113/645 (17.5 %) patients were reported or observed. All of these events were non-serious. "
Milvio 1984	Nimesulide vs benzydamine	Counts of SAEs	Not explicitly reported	The study reports that "[n]imesulide was generally very well tolerated. Only one patient suffered from moderate gastric pyrosis and drowsiness."
Nouri 1993	Nimesulide vs	Counts of SAEs	Not explicitly reported	The study notes that "[t]herapy with nimesulide was well tolerated and was not

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Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
	Naproxen			associated with adverse reactions. In the naproxen group, however, 2 patients experienced episodic gastralgia of moderate intensity, one starting on the third, and the other on the eighth day of therapy. Laboratory parameters were not modified by either treatment."
Ottaviani 1993	Nimesulide	Counts of SAEs	Nimesulide: 10 SAEs out of 940 patients	The study reports that „[t]he drug was well tolerated, and of the 75 patients who reported adverse effects, only 26 had to be withdrawn from treatment. (…) Physicians' assessments of therapeutic efficacy and tolerability of treatment were good in most patients". The SAEs reported included „[w]ater retention, sweating, flush, loss of appetite, vision disturbance, (…) [h]eartburn, gastralgia, dyspepsia, nausea, (…) [v]ertigo, (…) [r]ash [and] urticaria."
Schachtel 1988	Ibuprofen vs acetaminophen (paracetamol) vs placebo	Counts of AEs	Not explicitly reported	The study reports that "[n]o adverse effects were reported during the study." The study provides only very little detail on whether and how SAEs were monitored.
Schachtel 1991	Aspirin vs placebo	Counts of SAEs	Not explicitly reported	The study reports that "[o]f the 210 patients admitted to the study, one patient (receiving aspirin) was discontinued after 1 hour because of an adverse effect (nausea and vomiting) (…). There were no other side effects or exclusions from the trial."
Schachtel 2007	Valdecoxib vs placebo	Counts of SAEs	Valdecoxib (high dose): 0 SAEs Valdecoxib (low dose): 0 SAEs Placebo: 0 SAEs	The study reports that "[t]here were no serious adverse events, and no patient discontinued the study as a result of an adverse event."
Schachtel 2011	Celecoxib vs Celecoxib + Placebo vs Placebo	Counts of SAEs	Celecoxib (low dose + low dose): 0 SAEs Celecoxib (low dose + high dose): 0 SAEs	The study reports that "[t]here were no serious AEs, deaths, or discontinuations due to an AE. Overall, the incidence of AEs was similar among the 4 treatment groups."

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Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
			Celecoxib (low dose) + Placebo: 0 SAEs Placebo: 0 SAEs	
Smith 2014	Ibuprofen + caffeine vs ibuprofen vs caffeine vs placebo	Counts of SAEs	Not explicitly reported	The study reports that "[t]here were no serious adverse events reported, and studymedication was well tolerated."
Sperber 1989	Pseudoephidrine + ibuprofen vs pseudoephidrine vs placebo	Count of SAEs	Not explicitly reported	The study notes that both drugs "were generally well tolerated. No subjects withdrew from the study due to adverse drug effects." The study mentions the following "possible adverse effects of treatment": "Lightheadedness, Difficulty sleeping, Lethargy, Indigestion".
Sperber 1992	Naproxen vs placebo	Counts of SAEs	Not explicitly reported	The study reports that "[s]ide effects to naproxen were not noted in any of the three cohorts. One volunteer in the naproxen group experienced gastrointestinal symptoms after two doses of the drug, but after missing two doses, completed treatment without incident. Two volunteers receiving placebo had gastrointestinal complaints."
Weckx 2002	Celecoxib (1x daily) vs celecoxib (2x daily) vs diclofenac	Counts of SAEs	Celecoxib (1x): 0 SAEs Celecoxib (2x): 0 SAEs Diclofenac: 0 SAEs	Study reports that "[n]o serious adverse events were recorded."
Younkin 1983	Apsirin vs amantadine (1x daily) vs amantadine (2x daily)	Counts of SAEs	Not explicitly reported	The study reports that "[a] number of volunteers in all groups experienced a symptomatic complaint on at least one occasion that they attributed to the medication. In the aspirin treatment group, the subjects took all tablets, but six did not take all prescribed capsules. All subjects took all medications the first 3 days of the study. Six patients also had at least one episode of insomnia, nausea, or tinnitus."

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Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
Comparison of ibuprofen with acetaminophen (paracetamol): Effects on the rate of reconsultations				
Little 2013	Ibuprofen vs Paracetamol vs Ibuprofen + Paracteamol	Healthcare utilization: return visit with new or worsening symptoms or complicationsof intervention	Ibuprofen risk of reconsultation: 20%; Paracetamol risk of reconsultation: 12%; Ibuprofen + Paracetamol risk of reconsultation: 17% aRR(Ibuprofen vs Paracetamol) = 1.67 (1.12-2.38)	For the outcome reconsultation (with new or unresolved symptoms or complications within one month), the study reports 35/300 (11%) events in the paracetamol group, 58/295 (20%) in the ibuprofen group and 48/285 (17%) for the combined ibuprofen/paracetamol group. The adjusted risk ratio for the ibuprofen vs. the paracetamol group was 1.67 (95% CI: 1.12 to 2.38; p-value: 0.012). The study reports that "[m]ost of the 17 "complications" recorded were not serious, and three could be classified as reconsultations based on the baseline case record form."

11. Characteristics of and outcomes reported in studies included in the evidence mapping

Study ID	Study title	Study design	Partici-pants (n)	Follow up	Drugs	Disease / pathogen	Adverse outcome reporting	Reporting on adverse outcomes
Aksoylar 1997	Evaluation of sponging and antipyretic medication to reduce body temperature in febrile children	RCT	224	3 hours	Sponging alone vs. Sponging with a single oral dose of aspirin 15 mg/kg, or paracetamol 15 mg/kg, or ibuprofen 8 mg/kg	URTI, Pneumonia, Otitis media, gastroenteritis, UTI, Others	The study explicitly reports that there were no severe adverse outcomes;	"No serious side effects were observed that required stopping the treatment."

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Autret 1997	Evaluation of ibuprofen versus aspirin and paracetamol on efficacy and comfort in children with fever	RCT	351	5 days	Ibuprofen vs. Aspirin vs. Paracetamol	Fever	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"Of the 348 patients included, 14 patients experienced 18 adverse effects. […] In the ibuprofen group, 9 patients reported 13 adverse effects, 1 of which was experienced twice. In the paracetamol group, one child had one adverse effect and in the aspirin group four patients had four adverse effects."
Autret-Leca 2007	Ibuprofen versus paracetamol in pediatric fever: objective and subjective findings from a randomized, blinded study	RCT	301	3 days	Acetaminophen vs. Ibuprofen	Fever	The study explicitly reports severe adverse outcomes;	"All adverse events reported were either mild or moderate in severity. One serious adverse event was reported in a patient after having taken seven doses of randomized treatment (paracetamol) on the first day. The child was suffering from persistence of wavering fever and onset of cough – an X-ray revealed pneumopathy. The child recovered 4 days later but withdrew from the trial. The event was recorded as having no relationship to study drug."
Barberi 1993	Double-Blind Evaluation of Nimesulide vs Lysine-Aspirin in the Treatment of Paediatric Acute Respiratory Tract Infections	RCT	70	5 days	Nimesulide vs. Lysine-aspirin	Acute infection and inflammation of the respiratory tract (laryngitis, tracheitis, bronchitis, pneumonia)	The study explicitly reports on mild or moderate adverse outcomes, but does	"Gastrointestinal adverse events were observed in 11 patients (3 treated with nimesulide and 8 treated with lysine-aspirin), but none required withdrawal from therapy. In addition, no significant changes in laboratory

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							not mention severe adverse outcomes;	tests were observed with either drug (p >0.05)."
Bertin 1991	Randomized, double-blind, multicenter, controlled trial of ibuprofen versus acetaminophen (paracetamol) and placebo for treatment of symptoms of tonsillitis and pharyngitis in children	RCT	231	48 hours	Ibuprofen vs. Acetaminophen and placebo	Sore throat related to tonsillitis or pharyngitis	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"Twelve children had mild side effects: five of these were in the Placebo group (nausea, abdominal pain, and two cutaneous rashes), three of these were in the acetaminophen group (nausea), and five of these were in the ibuprofen group (nausea and abdominal pain). No other side effects were reported. Treatment was never interrupted because of side effects."
Cappella 1993	Efficacy and Tolerability of Nimesulide and Lysine Acetylsalicylate in the Treatment of Paediatric Acute Upper Respiratory Tract Inflammation	RCT	70	4.5 days	Nimesulide vs. Lysine-acetylsalicylate	URTI and fever	The study explicitly reports that there were no adverse outcomes (without specifying their severity);	"There were no relevant adverse effects observed during treatment or significant changes in the haematological profile in any patient."

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Choi 2018	The antipyretic efficacy and safety of propacetamol compared with dexibuprofen in febrile children: a multicenter, randomized, double-blind, comparative, phase 3 clinical trial	RCT	311	3 days	Propacetamol vs. Dexibuprofen	Fever due to URTI	The study explicitly reports that there were no severe adverse outcomes;	"A total of 84 adverse events in 64/263 patients were reported. Adverse events included vomiting, diarrhea, abdominal pain, constipation, rash, elevated liver enzyme, and thrombocytopenia. [...] There were no serious adverse events in which the patient(s) had been exposed to a danger to life, required a longer hospital stay, or had acquired permanent or major sequalae."
Erlewyn-Lajeunesse 2006	Randomised controlled trial of combined paracetamol and ibuprofen for fever	RCT	123	1hour	Paracetamol vs. Ibuprofen vs. Both	Fever	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	One child experienced a rapid temperature drop from 39.5°C to 37.7°C in one hour. She was admitted for observation and recovered spontaneously. “One child in the paracetamol group received a dose of 27.8 mg/kg in error. The child did not suffer any adverse consequences from this overdose. There were no other adverse events.”
Figueras Nadal 2002	Effectiveness and tolerability of ibuprofen-arginine versus paracetamol in children with fever of likely infectious origin	RCT	187 ITT	8 hours	Ibuprofen + arginine vs. Paracetamol	Fever due to: Upper RTI, Lower RTI, Gastrointestinal infection, Upper UTI, Soft tissue Infection, Otitis, Other	The study explicitly reports that there were no severe adverse outcomes;	"Nineteen patients (9.5%) experienced a total of 19 adverse events, 10 of them in the ibuprofen-arginine group and 9 following paracetamol administration, with a mild to moderate intensity. No serious adverse events were reported within the study period. One patient presented with

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								neutropenia prior to the first intake of paracetamol and this was consequently considered as unrelated to the study medication."
Gelotte 2010	Multiple-Dose Pharmacokinetics and Safety of an Ibuprofen–Pseudoephedrine Cold Suspension in Children	Open-label safety study, uncontrolled	114	4 days	Ibuprofen-pseudoephedrine suspension	Rhinitis	The study explicitly reports that there were no severe adverse outcomes;	"A total of 18.4% (21/114) of subjects reported 1 or more adverse events; none were classified as serious. [...] Drug-related adverse events, that is, those that were classified by the investigator as definitely, probably, possibly, or of unknown relationship to study drug, were reported by 13.2% (15/114) of subjects (data not provided). All but 1 adverse event (cough increased) was mild or moderate in intensity."
Gianiorio 1993	Antipyretic and Anti-Inflammatory Efficacy of Nimesulide vs Paracetamol in the Symptomatic Treatment of Acute Respiratory Infections in Children	RCT	40	7 days	Nimesulide vs. Paracetamol	LRTI	The study explicitly reports that there were no adverse outcomes (without specifying their severity);	"No adverse reactions, abnormal physical findings or abnormal laboratory results attributable to either nimesulide or paracetamol were observed."
Goyal 1998	Double Blind Randomized comparative evaluation of nimesulide and paracetamol as antipyretics	RCT	99	3 days	Nimesulide vs. Paracetamol	Fever	The study explicitly reports on mild or moderate adverse	"Adverse reactions were seen in the form of epigastric pain and vomiting in one patient in nimesulide group and three patients in paracetamol group."

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							outcomes, but does not mention severe adverse outcomes;	
Hadas 2011	Premarketing Surveillance of Ibuprofen Suppositories in Febrile Children	Safety study, uncontrolled	490	7 days	Ibuprofen suppositories	Fever	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"Adverse reactions were reported in 8 patients (1.63%, 95% confidence interval = 1.77-3.25). The most common adverse event was diarrhea: 4 children (0.8%, 95% confidence interval = 0.24-2.2) had diarrhea immediately after the administration of the drug. Two children developed a rash, 1 child had shivering, and 1 child had rectal burning after suppository administration."
Hay 2008	Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): randomised controlled trials	RCT	156	5 days	Combination of paracetamol and ibuprofen vs. Paracetamol vs. Ibuprofen	Fever	The study explicitly reports severe adverse outcomes;	Parents recorded adverse effects. "The most common adverse effects were diarrhoea and vomiting, which were equally distributed between groups. The overall number of children experiencing adverse events was, however, too small to make meaningful comparisons between treatments. Five children were admitted to hospital (constituting serious adverse events)": PCM group: 1, ibuprofen group: 3, PCM plus ibuprofen group: 1 child.

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Jayawar-dena 2017	Antipyretic Efficacy and Safety of Ibuprofen Versus Acetaminophen Suspension in Febrile Children: Results of 2 Randomized, Double-Blind, Single-Dose Studies	RCT	333	8 hours	Ibuprofen vs. Acetaminophen	Fever	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"In total, 7.5% of patients in each treatment group had AEs. In the IBU group, 1 incidence each of headache, vomiting, and rash were considered related to the study drug. In the APAP group, 3 incidences of vomiting were considered related to the study drug."
Kandoth 1984	Comparative Evaluation of Antipyretic Activity of Ibuprofen and Aspirin in Children with Pyrexia of Varied Aetiology	Cross-over study	28	2 days	Ibuprofen vs. Aspirin	URTI, Bronchitis, Pyrexia of unknown origin, Malaria, Miscellaneous	The study explicitly reports that there were no adverse outcomes (without specifying their severity);	"In this single-dose study no side-effects were observed with either drug."

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Kauffman 1992	Antipyretic Efficacy of Ibuprofen vs Acetaminophen	RCT	38	24 hours	Ibuprofen vs. Acetaminophen vs. Placebo	Fever without apparent focus of infection (n=8); herpetic stomatitis (n=1); otitis media (n=7); acute pharyngitis (n=10); pneumonia (n=3); acute sinusitis (n=1); and viral upper respiratory tract infection (n=7)	The study explicitly reports that there were no adverse outcomes (without specifying their severity);	"No adverse reactions, abnormal physical findings, or abnormal laboratory results attributable to either ibuprofen or acetaminophen were observed."
Khalil 2017	A multicenter, randomized, open-label, active-comparator trial to determine the efficacy, safety, and pharmacokinetics of intravenous ibuprofen for treatment of fever in hospitalized pediatric patients	RCT	121	up to 5 days	Ibuprofen (intravenous) vs. Acetaminophen	Fever	The study explicitly reports severe adverse outcomes;	"Adverse events were reported for 54 of the 100 patients, with most (97%) being classified as mild to moderate in severity. [...] There were no deaths reported in this study. There were four (4%) subjects for whom six serious adverse events were reported. In the intravenous ibuprofen group, two subjects experienced four serious adverse events; one with pancreatitis and hepatitis and one with cardiac arrest and pneumothorax. In the acetaminophen group, two (2%) subjects experienced two serious adverse events; pleural effusion, and intra-abdominal abscess. None of the serious adverse events were deemed related to either intravenous ibuprofen or acetaminophen in the opinion of an independent

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								data safety monitor."
Kim 2013	Dexibuprofen for fever in children with upper respiratory tract infection	RCT	260	4 hours	Dexibuprofen (two different doses) vs. Ibuprofen	URTI	The study explicitly reports that there were no severe adverse outcomes;	"There were no significant differences in number of AE experienced (P = 0.98), nor were there differences in number of patients experiencing AE in each group (DEX 1, n = 33; DEX 2, n = 34; control, n = 35). When AE were classified according to severity (grades 1–5; data not shown), there were no differences in severity between the three groups. Of the 159 AE, all but three were grade 1 or 2. Of these three, two were fever and one was coughing."
Kramer 2008	Alternating Antipyretics: Antipyretic Efficacy of Acetaminophen Versus Acetaminophen Alternated With Ibuprofen in Children	RCT	36	6 hours	Ibuprofen alternated with acetaminophen vs. acetaminophen alone	Fever	The study explicitly reports on mild or moderate adverse	"During the study period, 8 (21%) of all patients had symptoms including diarrhea, flatulence, emesis, decreased appetite, epigastric pain, nausea, headache, and

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							outcomes, but does not mention severe adverse outcomes;	insomnia. These symptoms did not prevent any of the patients from taking the study medications. There were no differences between groups in the incidence of any of these potential side effects."
Lal 2000	Antipyretic effects of nimesulide, paracetamol and ibuprofen-paracetamol	RCT	89	5 days	Nimesulide vs. Paracetamol vs. Ibuprofen + paracetamol	URI and LRI	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"As far as the monitoring of other ADR was concerned, only a few adverse effects namely, epigastric pain, vomiting were encountered and on comparing it in different groups, no marked difference was found."
Lee 2015	Single intramuscular injection of diclofenac sodium in febrile pediatric patients	Cohort study	300	2 days	Diclofenac sodium	Febrile illness	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"One patient developed hypothermia 4 h following injection of diclofenac sodium" "no asthmatic attacks occurred in the emergency room during the observation" "Two patients with a history of asthmatic bronchitis had wheezing" "there were no reported allergic reactions"
Luo 2017	Alternating Acetaminophen and Ibuprofen versus Monotherapies in	RCT	474	24 hours	Acetaminophen + ibuprofen vs. Acetaminophen	Febrile illness (due to suppurative tonsillitis, URTI,	The study explicitly reports on	"No obvious toxicities were observed" "Asthma": 2/157 in ibuprofen

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	Improvements of Distress and Reducing Refractory Fever in Febrile Children: A Randomized Controlled Trial				vs. Ibuprofen	acute bronchitis, herp angina, hand foot and mouth disease, angina subitum)	mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	group vs 0/156 in paracetamol and 0/158 in alternating group"
Marriott 1991	A dose ranging study of ibuprofen suspension as an antipyretic	RCT	93	12 hours	Ibuprofen (4 different doses)	Fever	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"A total of 19 adverse clinical events were recorded in 17 children during the study periods. Five children vomited, seven children had behavioural changes ranging from 'more miserable' to 'delirious', there were five febrile convulsions (all in children admitted following a febrile convulsion), one child developed diarrhoea, and one child manifested a rash."
McIntyre 1996	Comparing efficacy and tolerability of ibuprofen and paracetamol in fever	RCT	150	3 days	Ibuprofen vs. Paracetamol	Febrile convulsion, viral illness (non-specific), chest infection, asthma/wheezing, croup, gastroenteritis, bronchiolitis, soft tissue infection, urinary tract infection, otitis media, tonsillitis, herpes stomatitis,	The study explicitly reports severe adverse outcomes;	"Seven patients in the ibuprofen group and eight in the paracetamol group withdrew due to adverse events and/or lack of efficacy." AE ibuprofen group: urticarial rash, vomiting, abdominal pain and sore throat, AE PCM group: nose bleed, purpuric spots at the site of the blood pressure cuff, and meningococcal meningitis. "Twenty four out of 150 patients (16%) experienced 34

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						septic arthritis, tracheitis, septicaemia		adverse events during the study: 10/76 patients (13%) in the ibuprofen group had 16 events and 14/74 patients (19%) in the paracetamol group had 18 events."
Nabulsi 2006	Alternating ibuprofen and acetaminophen in the treatment of febrile children: A pilot study	RCT; in regard to NSAID: cohort study	70	8 hours	Ibuprofen + acetaminophen vs. Ibuprofen + placebo	Febrile illness	The study explicitly reports that there were no severe adverse outcomes;	"No serious adverse reactions were observed in these subjects. In addition, none of the subjects developed any symptom or sign suggestive of gastrointestinal, hepatic or renal toxicity."
Polidori 1993	A Comparison of Nimesulide and Paracetamol in the Treatment of Fever Due to Inflammatory Diseases of the Upper Respiratory Tract in Children	RCT	110	6 days	Nimesulide vs. Paracetamol	Tonsillitis, Laryngitis, Pharyngitis, Otitis, Tracheitis, Bronchitis, Exanthema	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"Three patients treated with nimesulide and 6 patients treated with paracetamol withdrew from therapy because of urticaria, vomiting or diarrhoea."
Prado 2006	Antipyretic efficacy and tolerability of oral ibuprofen, oral dipyrone and intramuscular dipyrone in children: A randomized controlled trial	RCT	75	2 hours	Ibuprofen vs. Dipyrone (two different doses)	URI and LRI	The study explicitly reports on mild or moderate adverse outcomes, but does not	"There was only one case of mild, transient urticaria, which appeared 30 minutes after oral ibuprofen administration in a girl aged 9.1 months. [...] The urticaria remitted by the time of reaching three hours after ibuprofen administration, without any specific therapy."

							mention severe adverse outcomes;	
Ruperto 2011	A randomized, double-blind, placebo-controlled trial of paracetamol and ketoprofren lysine salt for pain control in children with pharyngotonsillitis cared by family pediatricians	RCT	97	4 days	Paracetamol vs. Ketoprofen vs. Placebo	Pharyngotonsillitis	The study explicitly reports that there were no severe adverse outcomes;	"Safety evaluations at 1, 4 hours after administration was rated good or very good by parents, investigators and children in more than 90% of the cases for both paracetamol and placebo. No serious adverse events occurred. Four adverse events were observed in 4 patients: bronchitis and rash in the ketoprofen lysine salt group, diarrhoea and cough in the placebo group"
Salmon Rodriguez 1993	Assessment of the efficacy and safety of nimesulide vs naproxen in pediatric patients with respiratory tract infection	RCT	99	8 days	Nimesulide vs. Naproxen	Pharyngo-amygdalitis	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"In this study, more adverse events were observed with naproxen than with nimesulide." Most were gastrointestinal (4 nimesulide recipients and 13 naproxen recipients [$p < 0.05$, Chi^2-test]). "Several naproxen recipients reported more than 1 adverse event [...] Furthermore, urinalysis revealed a significant ($p = 0.04$) increase in proteinurea for patients treated with naproxen compared with those treated with nimesulide."
Sarrell 2006	Antipyretic treatment in young children with fever	RCT	480	14 days	Acetaminophen vs. Ibuprofen vs. Alternated acetaminophen	Fever due to: URI, AOM, Pharyngitis, Bronchiolitis, Gastroenteritis,	The study explicitly reports that there	"None of the patients in any of the groups had a drug-related adverse event or serious illness. Mild elevation in levels of liver

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					and ibuprofen	Viral illness	were no severe adverse outcomes;	enzymes and renal findings were observed in 8 children (1.7%) and 14 children (3.0%), respectively, but none of the acute-stage laboratory abnormalities persisted to the 14-day follow-up evaluation, and there were no statistically significant differences among the groups (P=.60 for abnormal liver function and P=.93 for abnormal renal function)."
Senel 2012	Comparison of Acetaminophen and Ketoprofen in Febrile Children: A Single Dose Randomized Clinical Trial	RCT	316	6 hours	Ketoprofen vs. Acetaminophen	Fever	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"In the present study only one patient had an allergy favoring urticaria in the ketoprofen group."
Sheehan 2016	Acetaminophen versus Ibuprofen in Young Children with Mild Persistent Asthma	RCT	300	46 weeks	Ibuprofen vs. Acetaminophen	Pain or fever	The study explicitly reports severe adverse outcomes	"No significant between-group differences were observed with respect to adverse events or serious adverse events. Six serious adverse events occurred in the acetaminophen group and 12 in the ibuprofen group. No deaths from any cause occurred during the trial."
Simila 1976	Oral Antipyretic Therapy: Evaluation of Ibuprofen	nRCT	79	6 hours	Ibuprofen vs. Indomethacin vs.	Fever mostly due to respiratory	The study explicitly	"No side effects from the drugs were seen in this series of

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					Aspirin vs. Paracetamol vs. Aminophenazone	infection	reports that there were no adverse outcomes (without specifying their severity)	patients."
Ugazio 1993	Clinical and pharmacokinetic study of nimesulide in children	RCT (not blinded)	100	up to 9 days	Nimesulide oral suspension vs. Paracetamol	Acute URTI and fever	The study explicitly reports that there were no adverse outcomes (without specifying their severity);	"there were no drug-related adverse events recorded"
Ulukol 1999	Assessment of the efficacy and safety of paracetamol, ibuprofen and nimesulide in children with upper respiratory tract infections	RCT (not blinded)	90	up to 5 days after discharge	Paracetamol, ibuprofen vs. Nimesulide	Acute URTI and fever	The study explicitly reports that there were no adverse outcomes (without specifying their severity);	"Paracetamol, ibuprofen and nimesulide were remarkably well tolerated and there were no drug-related side effects recorded, including haematological abnormalities and hepatotoxicity."
Van Esch 1995	Antipyretic Efficacy of Ibuprofen and Acetaminophen in Children With Febrile Seizures	RCT	71	24 hours	Ibuprofen vs. Acetaminophen	Febrile seizure	The study explicitly reports on mild or moderate	"Fourteen adverse events were recorded in nine patients. [Ibuprofen treatment: 6; acetaminophen treatment: 8 ....] The other adverse events

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							adverse outcomes, but does not mention severe adverse outcomes;	were [two] gastrointestinal complaints (acetaminophen), exanthemas [ibuprofen: 1, acetaminophen: 2], insomnia (ibuprofen), and hypothermia [ibuprofen: 2, acetaminophen: 1]."
Vauzelle-Kervroedan 1996	Antipyretic efficacy of tiaprofenic acid in febrile children	RCT	55	48 hours	Tiaprofenic acid vs. Placebo	Fever	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"Five (9.1%) children had vomited during the six hour period after dosing: 3 in the [placebo] group, and 2 in the TA group" [...] "No major side effect was reported by the parents during the study period"
Vauzelle-Kervroedan 1997	Equivalent antipyretic activity of ibuprofen and paracetamol in febrile children	RCT	116	2-4 days	Ibuprofen vs. Acetaminophen	Fever	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"Two children vomited during the study (1.7%), both of whom had received paracetamol."
Vyas 2014	Randomized comparative trial of efficacy of paracetamol,	RCT	99	4 hours	Paracetamol vs. Ibuprofen vs.	Upper respiratory infection, lower	The study explicitly	"No serious or severe adverse events were noted in any of the

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	ibuprofen and paracetamol-ibuprofen combination for treatment of febrile children				Combination	respiratory infection, viral illness, bronchiolitis	reports that there were no severe adverse outcomes;	groups. [...] In the ibuprofen group, three patients out of 32 had experienced the adverse events; one had nausea, one abdominal pain and one had maculopapular skin rash. All the three adverse events were mild with a possible relationship to treatment. In the combination group, four patients out of 31 had experienced the adverse events. One patient had vomiting, which was mild with doubtful relationship to treatment. Two patients had abdominal pain and one patient had a skin rash, which were mild with a possible relationship to treatment."
Walker 1986	Comarative Efficacy Study of Chewable Aspirin and Acetaminophen in the Antipyresis of Children	RCT	46	4 hours	Aspirin vs. Acetaminophen	Fever	The study explicitly reports that there were no adverse outcomes (without specifying their severity);	"Adverse effects were not observed with either drug."
Walson 1989	Ibuprofen, acetaminophen, and placebo treatment of febrile children	RCT	118	48 hours	Ibuprofen suspension vs. Acetaminophen elixir vs. Placebo liquid	Fever	The study explicitly reports on mild or moderate adverse	"The most common of all adverse experiences that appeared to be drug related (p= 0.07) were mild gastrointestinal symptoms. These occured in 10 of the 32 patients who received

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							outcomes, but does not mention severe adverse outcomes;	5 mg/kg ibuprofen, 6 of the 28 who received 10 mg/kg ibuprofen, 6 of the 33 who received 20 mg/kg acetaminophen, and 2 of the 34 patients who received placebo."
Walson 1992	Comparison of Multidose Ibuprofen and Acetaminophen Therapy in Febrile Children	RCT	64	48 hours	Ibuprofen vs. Acetaminophen	Fever	The study explicitly reports that there were no severe adverse outcomes;	Six children were withdrawn from the study, two because of dosing errors, three because of hypothermia (temperature of less than 35.6°C; all three patients were in the acetaminophen group), and one because of gastrointestinal distress (ibuprofen group). "No adverse effects of greater than moderate severity were reported."
Wilson 1991	Single-dose, placebo-controlled comparative study of ibuprofen and acetaminophen antipyresis in children	non-randomised trial	178	12 hours	Ibuprofen suspension vs. Acetaminophen elixir vs. Placebo suspension	Fever	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	One child had transient hypothermia and profuse night sweats due to pulmonary tuberculosis and a second child had a transient drop in temperature below 36.1°C
Wong 2001	Antipyretic effects of dipyrone versus ibuprofen versus acetaminophen in children: results of a	RCT	628	14 days	Dipyrone vs. Acetaminophen vs. Ibuprofen	Fever	The study explicitly reports on mild or	"Most of the adverse events were gastrointestinal in nature, such as vomiting and diarrhea. Of the total adverse events

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	multinational, randomized, modified double-blind study						moderate adverse outcomes, but does not mention severe adverse outcomes;	within each group, those considered drug-related comprised 17% of the dipyrone, 15% of the acetaminophen, and 27 % of the ibuprofen groups. There were no statistically significant differences among the three groups with respect to the incidence of adverse events."
Yilmaz 2003	Intramuscular Dipyrone versus Oral Ibuprofen or Nimesulide for Reduction of Fever in the Outpatient Setting	RCT	252	2 hours	Ibuprofen vs. Nimesulide, dipyrone	Fever	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"An erythematous eruption occurred in only one mpatient who used nimesulide. The number of cases where the axillary temperature dropped below 36°C was 15 (17.9%) in the diphyrone group, six (7.1%) in the ibuprofen group, and three (3.6%) in the nimesulide group."
Yoon 2008	The effects and safety of dexibuprofen compared with ibuprofen in febrile children caused by upper respiratory tract infection	RCT	255	3 days	Dexibuprofen (two different doses) vs. Ibuprofen	Fever due to URTI	The study explicitly reports on mild or moderate adverse outcomes, but does not mention severe adverse outcomes;	"In 255 children, 49 adverse drug reactions of mild to moderate level were reported in 32 children (12.7%) during the study [...] The adverse reactions included diarrhoea, constipation, nausea, vomiting, abdominal pain, decreased oral intake, irritability, facial oedema, skin rash, elevated liver enzyme level and thrombocytopenia"

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Yoshikawa 2001	Study of Influenza-Associated Encephalitis/Encephalopathy in Children During the 1997 to 2001 Influenza Seasons	Case series	20	Through disease course	Diclofenac sodium, acetaminophen, a combination of sulpyrine and acetaminophen, combination of acetaminophen and Mefenamic acid	Influenza	Three study explicitly reports severe adverse outcomes;	Only children with influenza-associated encephalitis/encephalopathy were studied. "Concerning the use of antipyretics, no patient had taken apsirin before the onset. Sixteen patients had taken some antipyretics before the onset of encephalitis/encephalopathy. Eight patients had received diclofenac sodium rectally..." "With regard to the use of antipyretics, all 5 deceased patients were given antipyretics, 3 having taken diclofenac sodium.. Five of the 7 patients who fully recovered had taken antipyretics (ie, 3 diclofenac sodium and 2 acetaminophen)."

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12. Sub-group analyses (table s1)

Table s1: Use of NSAIDs vs. no use of NSAIDs in adults with viral respiratory infections (subgroup analyses)

Patient or population: Adults with viral respiratory infections (Wen 2017; Wen 2018), adults with influenza (Epperly 2016)
Intervention: Use of NSAIDs
Comparison: No use of NSAIDs

Outcomes	Impact1	№ of participants (studies)	Certainty of the evidence (GRADE)2
1. Parenteral NSAIDs			
Ischemic stroke Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	Wen 2018 Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 4.24 (95% CI: 2.92-6.15) risk associated with ARI episode: aOR = 2.11 (95% CI: 1.91 - 2.34) risk associated with NSAID use: aOR = 2.67 (95% CI: 2.23 - 3.20)	23618 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
Hemorrhage stroke Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	Wen 2018 Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 9.71 (95% CI: 3.79-24.92) risk associated with ARI episode: aOR = 1.66 (95% CI: 1.33 - 2.06) risk associated with NSAID use: aOR = 3.71 (95% CI: 2.57 - 5.33)	(5900 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
Myocardial infarction Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	Wen 2017 Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 7.22 (95% CI: 4.07-12.81) risk associated with ARI episode: aOR = 2.65 (95% CI: 2.29-3.07) risk associated with NSAID use: aOR = 3.77 (95% CI: 2.85-5.02)	9793 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
2. High dose non-parenteral NSAIDs			
Ischemic stroke Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	Wen 2018 Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 2.28 (95% CI: 1.76-2.95) risk associated with ARI episode: aOR = 2.11 (95% CI: 1.91 - 2.34) risk associated with NSAID use: aOR =1.26 (95% CI: 1.13 - 1.41)	(23618 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]

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Hemorrhagic stroke Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	Wen 2018 Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 1.47 (95% CI: 0.85-2.52) risk associated with ARI episode: aOR = 1.66 (95% CI: 1.33 - 2.06) risk associated with NSAID use: aOR = 1.38 (95% CI: 1.09 - 1.76)	(5900 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
Myocardial infarction Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	Wen 2017 Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 3.32 (95% CI: 2.34-4.93) risk associated with ARI episode: aOR = 2.65 (95% CI: 2.29-3.07) risk associated with NSAID use: aOR =1.10 (95% CI: 0.92-1.32)	9793 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
3. Low dose non-parenteral NSAIDs			
Ischemic stroke Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	Wen 2018 Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 1.98 (95% CI: 1.70-2.32) risk associated with ARI episode: aOR = 2.11 (95% CI: 1.91 - 2.34) risk associated with NSAID use: aOR =1.28 (95% CI: 1.21 - 1.38)	(23618 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
Hemorrhagic stroke Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	Wen 2018 Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 1.97 (95% CI: 1.39-2.79) risk associated with ARI episode: aOR = 1.66 (95% CI: 1.33 - 2.06) risk associated with NSAID use: aOR = 1.31 (95% CI: 1.13 - 1.52)	(5900 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
Myocardial infarction Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	Wen 2017 Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 2.95 (95% CI: 2.31-3.75) risk associated with ARI episode: aOR = 2.65 (95% CI: 2.29-3.07) risk associated with NSAID use: aOR = 1.38 (95% CI: 1.23-1.54)	9793 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
4. Aspirin			
Mortality H1N1 Influenza Follow-up: 60 days following intensive care unit admission or until death or hospital discharge	Epperly 2016 Mortality risk associated with aspirin use: aRR = 1.1 (95% CI: 0.6-1.9)	683 (1 retrospective, registry-based cohort study)	⊕◯◯◯ VERY LOW [b]
5. Diclofenac			

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Myocardial Infarction Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	Wen 2017 Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 3.37 (95% CI: 2.24-5.07) risk associated with ARI episode: aOR = 2.65 (95% CI: 2.29-3.06) risk associated with NSAID use: aOR = 1.29 (95% CI: 1.06-1.58)	9793 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
6. Mefenamic acid			
Myocardial infarction Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	Wen 2017 Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 3.11 (95% CI: 1.85-5.25) risk associated with ARI episode: aOR = 2.65 (95% CI: 2.29-3.06) risk associated with NSAID use: aOR = 1.65 (95% CI: 1.17-2.31)	9793 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
7. Coxibs			
Myocardial infarction Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	Wen 2017 Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 2.90 (95% CI: 1.26-6.70) risk associated with ARI episode: aOR = 2.65 (95% CI: 2.29-3.06) risk associated with NSAID use: aOR = 1.43 (95% CI: 1.12-1.82)	9793 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
8. NSAIDs other than Coxibs, Mefenamic acid, or Diclofenac			
Myocardial infarction Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	Wen 2017 Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 2.76 (95% CI:1.97-3.87) risk associated with ARI episode: aOR = 2.65 (95% CI: 2.29-3.07) risk associated with NSAID use: aOR = 1.18 (95% CI: 1.02-1.35)	9793 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]
9. More than one NSAIDs			
Myocardial infarction Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients 365d before the event	Wen 2017 Compared to no use of NSAIDs in adults without ARI (baseline): risk associated with NSAID use and ARI episode: aOR = 3.37 (95% CI: 2.08-5.46) risk associated with ARI episode: aOR = 2.65 (95% CI: 2.29-3.07) risk associated with NSAID use: aOR = 1.62 (95% CI: 1.24-2.13)	9793 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]

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

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Explanations

[1]All ORs reported for Wen 2017 and Wen 2018 are adjusted for discordant use of concomitant medications. ORs reported for Epperly 2016 are adjusted for age, sex, and vaccination and health status. [2]All studies included for this comparison were non-randomized; thus each body of evidence started the GRADE assessment as low certainty.

a. Downgraded by one level for imprecision. The confidence interval for the OR of the combined exposure to NSAIDs and acute respiratory infections overlaps with the confidence interval of the OR for exposure to NSAIDs alone and to acute respiratory infections alone, indicating that the effects of NSAIDs on cardiovascular events in individuals with acute respiratory infections are unclear. Confidence intervals include the possibility of positive, null or negative effects of NSAIDs in individuals with acute respiratory infections. b. Downgraded by one level for imprecision. The confidence interval is wide and includes the possibility of positive, null or negative effects.

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13. Summary of Findings tables for children (table s2 and s3)

Table s2: Use of NSAIDs vs. no use of NSAIDs in children with viral respiratory infections

Patient or population: children (between 2 months and 16 years) with viral respiratory infections
Intervention: use of NSAIDs
Comparison: no use of NSAIDs

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)*
Mortality H1N1 influenza Follow-up: up to 90 days following intensive care unit admission or until death or hospital discharge	**Epperly 2016** Risk associated with NSAIDs use: aRR = 1.5 (CI: 95%: 0.7-3.2)	838 (1 retrospective, registry-based cohort study)	⊕◯◯◯ VERY LOW [a]
Empyema Viral respiratory infections Follow-up: 15 days (from time of infection onset to empyema (cases) or to definition of control (controls))	**Le Bourgeois 2016** Risk associated with NSAIDs use: aOR = 2.79 (95% CI: 1.4-5.6)	166 (1 matched case-control study)	⊕◯◯◯ VERY LOW [b]
Acute gastrointestinal bleeding Viral respiratory infections Follow-up: 4 weeks (retrospective)	**Grimaldi-Bensouda 2010** Risk associated with NSAIDs use: aOR = 8.2 (95%CI: 2.6-26.0)	177 (1 case-crossover study)	⊕◯◯◯ VERY LOW [a]

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

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

Explanations
a. Downgraded evidence by 1 level for imprecision.
b. Downgraded evidence by 1 level for study limitations (risk of protopathic bias).

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Table s3: Use of ibuprofen vs. acetaminophen in children with fever

Patient or population: children (aged between 6 months and 12 years) with viral respiratory infections
Intervention: use of ibuprofen
Comparison: use of acetaminophen

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Death from any cause Follow-up: 4 weeks	**Lesko 1995** 1 death as consequence of car crash in acetaminophen group (1/28,130) 1 death from meningitis in the ibuprofen group (1/55,785)	83915 (1 RCT)	⊕⊕⊕⊕ HIGH
Hospitalization for any cause Follow-up: 4 weeks	**Lesko 1995** Relative risk of hospitalization for any cause: 0.99 (95% CI: 0.83-1.17)*	83915 (1 RCT)	⊕⊕⊕◯ MODERATE [a]
Acute gastrointestinal bleeding Follow-up: 4 weeks	**Lesko 1995** Risk of acute gastrointestinal bleeding in the ibuprofen group: 7.2 per 100 000 (95% CI: 2 to 18 per 100 000) Risk of acute gastrointestinal bleeding in the acetaminophen group: 0 per 100 000 (95% CI: 0 to 11 per 100 000)	83915 (1 RCT)	⊕⊕⊕◯ MODERATE [b]
Hospitalization for acute renal failure, anaphylaxis Follow-up: 4 weeks	**Lesko 1995** 0 events in either group	83915 (1 RCT)	⊕⊕⊕⊕ HIGH
Hospitalization for potentially serious adverse drug events (low white blood cell counts, erythema multiform, and serum sickness) Follow-up: 4 weeks	**Lesko 1995** Relative risk of hospitalization for potentially serious adverse drug events: 2.8 (95% CI: 0.61-12.5)*	83915 (1 RCT)	⊕⊕⊕◯ MODERATE [b]
Hospitalization for asthma Follow-up: 4 weeks	**Lesko 1995** Relative risk of hospitalization for asthma: 0.92 (95% CI: 0.56-1.52)*	83915 (1 RCT)	⊕⊕⊕◯ MODERATE [b]

***Calculations for this estimate were done by the review authors.**

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

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Explanations

a. Downgraded evidence by 1 level for study limitations: concerns for incomplete outcome reporting.

b. Downgraded evidence by 1 level for imprecision.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n.a.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n.a.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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