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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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5 6 7	2	patients with viral respiratory infections: Rapid systematic review				
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15 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

20 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.

Solution
 Solution<

2 3	40	Registration: Registered with PROSPERO (CRD42020176056) and the Open Science Framework
4 5	41	(osf.io/snrp4).
6 7	42	
8 9	43	Keywords: non-steroidal anti-inflammatory drugs, viral respiratory infections, adverse effects, side
10 11 12 13 14 15 16 17	44	effects, COVID-19
	45	
	46	Article Summary
18 19 20	47	Strengths and limitations of this study:
20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 546 47 48 49 50 51 52 53	48	• We conducted a rapid systematic review following Cochrane rapid review guidance and the
	49	PRISMA guideline
	50	We systematically searched three databases and conducted forward- and backward-citation
	51	searches
	52	• We followed a pre-specified protocol, and clearly state where we deviated from it
	53	• This is a rapid review, and we applied less quality controls than in the reviews we normally
	54	conduct
	55	• The review is limited to studies in patients with viral respiratory infections and conditions
	56	commonly caused by respiratory viruses; we excluded studies on adverse effects of NSAIDs in
	57	patients with bacterial respiratory infections, which have been summarised in existing reviews
	58	
	59	Wordcount: 3,454 words
	60	
	61	Background
54 55	62	
56 57	63	Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs, and have a
58 59	64	wide range of uses, including treatment of acute and chronic pain, fever, and inflammation. NSAIDs
60		3

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 bleeding¹ and renal damage,⁴ as well as elevated cardiovascular risks for some NSAIDs.¹⁵ 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

1 2 3	91	with viral respiratory infections on acute severe adverse events (including mortality, acute respiratory
5 4 5 6 7	92	distress syndrome, acute organ failure and opportunistic infections), acute healthcare utilization
	93	(including hospitalization, intensive care unit admission, supplemental oxygen therapy and mechanical
8 9	94	ventilation), as well as explicit quality of life measures and long-term survival.
10 11	95	
12 13 14 15	96	Methods
16 17 18	97	Protocol registration
19 20 21	98	The review was registered with PROSPERO (registration number: CRD42020176056) and the Open
21 22 23	99	Science Framework (osf.io/snrp4). Methods are based on Cochrane Rapid Review guidance. ¹⁸ Reporting
24 25	100	follows the PRISMA guideline.
26 27	101	
28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44	102	Search strategy and selection criteria
	103	
	104	We searched MEDLINE, EMBASE and the WHO COVID-19 database ¹⁹ up to 31 March 2020. We
	105	conducted forward- and backward-citation searches in Scopus using references of existing reviews and
	106	included studies. Our full search strategy is shown in the supplementary appendix.
	107	
	108	After removal of duplicate studies, titles and abstracts of all identified records were screened by one
45 46	109	review author to select records meeting our inclusion criteria. Subsequently, full texts were screened by
47 48	110	one review author. Twenty percent of all titles and abstracts, and 50% of all full texts were screened by a
49 50 51	111	second review author. We used Rayyan, a web-based application for title and abstract screening ²⁰ .
51 52 53	112	During full-text screening, we documented the reasons for exclusion.
54 55	113	
56 57	114	We included studies conducted in humans of any age with viral respiratory infections or conditions
58 59 60	115	commonly caused by respiratory viruses and exposed to systemic NSAIDs of any kind, reporting on acute
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1 2 3	116	severe adverse events, acute healthcare utilization, explicit quality of life measures or long-term surviva
4 5 6 7	117	We included studies reporting primary empirical data on at least 10 participants, except for studies o
	118	COVID-19, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS
8 9	119	where studies of any size were eligible. Tables 1 and 2 provide detailed inclusion and exclusion criteria.
10 11	120	
12 13	121	We included studies in which at least 50% of all patients in one of the study groups (intervention c
14 15 16	122	control group for randomised controlled trials (RCTs), and cases or controls for case control studies) me
17 18	123	our inclusion criteria (i.e. were adults, had a relevant infection or condition, and were exposed t
19 20	124	NSAIDs).
21 22	125	
23 24	126	We excluded studies in which patients received antibiotics as part of the intervention, taking antibioti
25 26 27	127	treatment as a proxy for bacterial infection. We did, however, include studies in which varying number
27 28 29	128	of participants received antibiotics independent of the intervention over the course of the study. ²¹ W
30 31	129	also included one study in patients with confirmed influenza infection who received an antibiotic as par
32 33	130	of their initial treatment regime. ²²
34 35	131	
36 37		
38 39	132	Data analysis
40 41 42	133	
42 43 44	134	One review author extracted data and assessed risk of bias of included studies using a pre-tested dat
45 46	135	extraction form (supplementary appendix). We used the Tool to Assess Risk of Bias in Case-Contro
47 48 49 50 51 52	136	Studies developed by the Clarity Group at McMaster University for case-control and case-crossove
	137	studies, ²³ and the Cochrane risk of bias tool adapted by the Cochrane Effective Practice and Organisatio
	138	of Care (EPOC) group for all remaining study designs. ²⁴ We applied GRADE to assess the certainty of
53 54 55	139	evidence, rating evidence as high, moderate, low or very low certainty. ²⁵
56 57	140	
58 59		
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141 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 .42 of detecting rare severe adverse events (i.e. case-control studies and large RCTs with > 1000 participants) 43 as these studies best addressed the commissioned review question. For the remaining studies in 44 .45 children, we mapped the evidence, i.e. we extracted and tabulated data on key study characteristics and .46 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 48 imaging findings), but decided that this was not feasible within the timeframe of the review. We had 49 intended to undertake meta-analyses and present forest plots of sufficiently similar studies. This was not .50 .51 feasible in view of substantial heterogeneity in the interventions and outcomes assessed. We therefore .52 summarised findings narratively and through tables.

We extracted and report all measures of treatment effect for the primary outcomes pre-specified in our .54 protocol. For dichotomous outcomes this includes risk ratios (RRs) and odds ratios (ORs). We extracted .55 and report adjusted results as provided by the included studies. We included 95% confidence intervals .56 (Cls) when these were reported by primary studies. .57

Availability of data and materials .59

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

Role of the funding source .62

64 This review was funded through staff positions and university funds at the Ludwig-Maximilians-65 Universität Munich, Germany. The review question was set by WHO, who requested this review from the .66 Chair of Public Health and Health Services Research at the LMU Munich in its capacity as a WHO

Collaborating Centre for Evidence-Based Public Health. The authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the WHO. Patient and public involvement Patients and the public were not involved in this study. Results **Results of the search** The PRISMA flow chart is shown in Figure 1, and the search log is shown in the 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 studies²⁶⁻²⁸ 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 study²⁷ and one RCT²¹ 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

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 RCTs²¹ ²² ³⁵⁻⁶⁰ and two cohort studies²⁶ 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 syncopation⁴³ 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

1 2 244						
3 4 5	245	One RCT in 889 patients aged 3 years or older with a follow-up of four weeks assessed effects on the rate				
5 6 7	246	of re-consultations with general practitioners. ²¹ Data on 595 patients were included in the analyses.				
8 9	247	Results indicate that in patients with acute respiratory infections ibuprofen is associated with a higher				
10 11 12 13 14 15 16	248	rate of re-consulations for new or unresolved symptoms or complications than paracetamol				
	249	(acetaminophen) (OR 1.7, 95% CI: 1.1 to 2.4). The study reports that "[m]ost of the 17 'complications'				
	250	recorded were not serious". ²¹ This evidence was considered to be of low certainty due to study				
17 18	251	limitations and indirectness of evidence.				
19 20	252					
21 22 23	253	Findings for children				
23 24 25	254					
26 27	255	Summary of findings for effects of NSAIDs on mortality and risk for empyema, gastrointestinal bleeding,				
28 29	256	death from all causes and hospitalisation in children are shown in Tables s1 and s2 in the supplementary				
30 31 32	257	appendix.				
33 34	258					
35 36 27	259	One cohort study in 838 children (mean age: 7 years) with a follow-up of 60 days reports effects on				
37 38	260	mortality. ²⁷ Results indicate that the effects of NSAIDs on mortality in critically ill children with H1N1				
39 40 41 42 43	261	influenza are unclear (aRR 1.5, 95% CI: 0.7-3.2; very low certainty evidence).				
	262					
44 45	263	One matched case-control study in 166 children aged 3-15 years with acute viral infections reports				
46 47 48	264	effects on risk for empyema (follow-up: 15 days). ³⁰ One case-crossover study in 177 children (aged 2				
48 49 50	265	months to 16 years) with fever reports effects on gastrointestinal bleeding (follow-up: 7 days). ²⁹ Results				
51 52	266	indicate that children with empyema and gastrointestinal bleeding may be more likely to have been				
53 54	267	exposed to NSAIDs than children without these conditions (aOR for empyema: 2.8, 95% CI: 1.4-5.6; aOR				
55 56 57	268	for gastrointestinal bleeding: 8.2, 95% CI: 2.6-26.0; very low certainty evidence). ^{29 30}				
57 58 59	269					
60		11				

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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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2 3	296	Evidence obtained for adults was of very low to low certainty, and should be interpreted with caution.
4 5 6 7	297	We did not find conclusive evidence for relevant effects of NSAIDs on mortality or other severe acute
	298	adverse outcomes in adults with viral respiratory infections. Low certainty evidence from one RCT
8 9 10	299	indicates that in participants aged 3 years and older with respiratory infections ibuprofen compared to
10 11 12	300	acetaminophen (paracetamol) is associated with a higher rate of re-consultations with general
13 14	301	practitioners. ²¹
15 16	302	
17 18 10	303	We identified 56 eligible studies in children. Most of these were small and of short duration, and provide
19 20 21	304	only limited evidence on severe adverse effects. One large RCT in children provides moderate to high
22 23	305	certainty evidence that the difference in the rate of death from all causes and of hospitalisation for acute
24 25	306	renal failure and anaphylaxis is likely to be smaller than 1 per 10,000, that the difference in
26 27 28	307	hospitalisation for acute gastrointestinal bleeding is likely to be smaller than 2 per 10,000, and the
28 29 30 31 32 33 34 35 36 27	308	difference in hospitalisation for any cause less than 20 per 10,000. ³¹⁻³⁴
	309	
	310	We did not identify any studies reporting on measures of inpatient healthcare utilisation, long-term
	311	survival or explicit quality of life measures.
37 38 39	312	
40 41 42 43	313	This is a rapid review, conducted over two weeks, with a number of limitations:
	314	• Searches were limited to three databases, i.e. MEDLINE, EMBASE and the WHO COVID-19
44 45	315	database, complemented with forward- and backward-citation searches. We did not search for
46 47 48	316	or include sources of grey literature or pre-prints, and considered only studies published in
48 49 50 51 52	317	English or German.
	318	• Screening criteria and guidance were refined and calibrated while screening was underway, and
53 54	319	only 20% of titles and abstracts and 50% of full texts were screened in duplicate.
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58 59		
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1 2 3	320	• Data extraction and risk of bias assessment were done by one review author only. To account for		
4 5	321	potential errors, all data presented in tables or figures as part of the evidence synthesis were		
6 7	322	checked for their correctness by a second review author.		
8 9	323	• Risk of bias assessment and full evidence synthesis was limited to studies in adults and to those		
10 11 12	324	studies in children most capable of detecting rare severe adverse events (i.e. case control studies		
12 13 14	325	and large RCTs). The decision to exclude other studies in children from evidence synthesis was		
15 16	326	taken post hoc.		
17 18	327	• All steps of the review process were undertaken rapidly, with fewer quality control measures		
19 20 21	328	than during the systematic reviews we usually conduct.		
22 22 23	329	• We were unable to undertake all the subgroup analyses foreseen in our protocol: many were not		
24 25	330	feasible due to too much heterogeneity between studies, for others (e.g. subgroup analyses by		
26 27	331	age or sex) we lacked the time.		
28 29	332			
30 31 32	333	The evidence identified in this review is also characterised by a number of limitations:		
33 34	334	• We included not only studies in patients with confirmed viral respiratory infections, but also		
35 36	335	studies in patients with conditions commonly caused by respiratory viruses, such as upper		
37 38	336	respiratory tract infections and fever in children. It is likely that not all participants of these		
39 40 41	337	studies had viral respiratory infections.		
42 43	338	• We did not consider studies on patients with bacterial infections; these can occur as a super-		
44 45	339	infection in patients with viral respiratory infections. Potential adverse effects of NSAIDs in		
46 47	340	patients with bacterial infections and conditions commonly caused by bacterial infections,		
48 49 50	341	including community-acquired pneumonia, have been summarised in existing reviews ⁶³ and		
50 51 52	342	were beyond the scope of this rapid review.		
53 54	343	• NSAIDs constitute a diverse group of drugs with diverging risk profiles for different populations		
55 56	344	and conditions. Not all studies distinguished between different types of NSAIDs. Some of the		
57 58				
59 60		4.4		
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1 2 3	345	older studies are likely to have included patients taking NSAIDs that are no longer available on				
4 346 the market due to their known side effects.						
6 7	347	• Some studies provided only indirect comparisons, which can be informative, but do not provide				
8 9	348	effect estimates for the actual comparison of interest, i.e. NSAID use vs. no NSAID use among				
10 11 12	349	individuals with a viral respiratory infection. ⁸⁹				
12 13 14	350	• We identified only one RCT that included a sufficiently large number of participants to identify				
15 16	351	rare severe adverse events. ³¹⁻³⁴ The remaining evidence derives from smaller RCTs, which are				
17 18	352	underpowered for detecting rare severe adverse events, and from case-control and cohort				
19 20 21	353	studies with methodological limitations.				
21 22 23	354					
24 25	355	Conclusions				
26						
27 28	356	We did not find conclusive evidence showing that NSAIDs in patients with viral respiratory infections are				
29 30 31	357	associated with additional risks for severe acute adverse outcomes, above and beyond the known risks				
31 32 33	358	associated with NSAIDs alone and viral respiratory infections alone. This absence of evidence should not				
34 35	359	be interpreted as evidence for the absence of such risks. Most of the evidence was of very low to low				
36 37	certainty, and should be interpreted with caution. The potential harms associated with NSAIDs must					
38 39	361	balanced with their potential therapeutic benefits. Existing guidance should be considered, including				
40 41 42	362	approved product information for specific NSAIDs and clinical guidelines on respiratory infections.				
43 44	363					
45 46	364	Captions:				
47 48	365	• Figure 1: PRISMA flow chart				
49 50 51	• Figure 2: Risk of bias of case-control and case-crossover studies					
52 53	367	• Figure 3: Risk of bias of studies other than case-control and case-crossover studies				
54 55	368	Table 1: Inclusion criteria				
56 57	369	Table 2: Exclusion criteria				
58 59						
60						
		15				

2 3	370	• Table	3: Summary of findings for the e	ffects of NSAIDs on mortality and cardiovascular events in
4 5	371	adults	s with viral respiratory infections	
6 7	372	• Table	4: Summary of findings for the e	ffects of NSAIDs on the rate of re-consultations with
8 9	373	gener	al practitioners in patients with a	acute respiratory infections
10 11 12	374			
13 14	375	Tables		
15	376			
16	377	Table 1		
17 18	378			
10	570			
20		Table 1: Inclusi	ion criteria	
21		Population	Humans of any age with acute	Patients with COVID-19 / SARS-CoV-2
22			viral respiratory infections, with	Patients with SARS / MERS
23			or without co-morbidities (e.g.	Patients with other coronavirus infections
24 25			cardiovascular disease, diabetes	Patients with other acute viral respiratory infections,
25 26			mellitus, COPD, asthma)	including influenza, parainfluenza and rhinovirus infections
20				Patients with conditions commonly caused by respiratory
28				viruses, including children with fever and patients of any
29				age with upper respiratory tract infections, including the
30				common cold, pharyngitis, laryngitis, sore throat and
31				tonsillitis, unless specified as being of bacterial etiology or
32				treated with antibiotics
33 34		Intervention	Non-steroidal anti-	Unselective COX inhibitors: ibuprofen, aspirin
34 35		/ Exposure	inflammatory drug (NSAID)	(acetylsalicylate), diclofenac, naproxen, indomethacin and
36			intake prior or during the acute	ketoprofen, etc.
37			infection, including oral,	4
38			intravenous and intramuscular	
39			NSAIDs and NSAIDs as	Selective COX 2 inhibitors: Celecoxib, Rofecoxib, Etoricoxib,
40			suppositories taken or administered for any reason	Lumiracoxib, and Valecoxib, etc.
41			(including treatment of	
42 43			underlying conditions, and	
44			treatment of fever, pain and	
45			other acute symptoms)	
46		Comparison	No or different NSAID	No NSAID (including other antipyretic and analgesic drugs,
47				e.g. paracetamol/ acetaminophen)
48				Different dose or application of NSAID
49 50				Different NSAID (e.g. aspirin versus ibuprofen)
50 51		Outcomes	Acute severe adverse events,	Acute severe adverse events:
52			acute healthcare utilization and	Mortality
53			longer-term effects	Acute respiratory distress syndrome (ARDS)
54				• Acute organ failure (including acute renal failure)
55				Cardiovascular events
56				Opportunistic infections
57 50				Severe acute allergic and hypersensitivity reactions
58 59				Other, as reported
60				Acute healthcare utilization:

 Rate and length of intensive care unit (ICU) utilizatio Rate and length of supplemental oxygen therapy Rate, length and type of mechanical ventilation (invasive vs. non-invasive) Other, as reported Longer-term effects:
 Rate, length and type of mechanical ventilation (invasive vs. non-invasive) Other, as reported
(invasive vs. non-invasive)Other, as reported
Other, as reported
Longer-term effects:
Explicit quality of life measures
 Long-term survival
study 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)

382 Table 2

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 /	NSAIDs no longer approved or marketed in key markets (e.g. US, Europe)
Exposure	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 inhibit 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 condition outside the scope of this review
Study designs	 Implicit quality of life measures (e.g. pain, nasal congestion) Non-empirical studies (e.g. commentaries)
	Animal studies
	Mechanistic data

51 384 52 385

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Table 3

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
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
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
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

assessment as low certainty.

1					
2 3 4 5 6 7 8 9 10		GRADE Working Group grades of evidence High certainty: We are very confident that the Moderate certainty: We are moderately confi estimate of the effect, but there is a possibility Low certainty: Our confidence in the effect es the estimate of the effect Very low certainty: We have very little confide different from the estimate of effect	ident in the effect estimate: The true effec y that it is substantially different timate is limited: The true effect may be s	t is likely to be ubstantially dif	close to the ferent from
11	388	Explanations: a. Downgraded by 1 level fo	r imprecision.		
12 13	389				
14 15	390 391	Table 4			
16 17 18 19	391	Table 4: Use of ibuprofen vs. paracetamo infections	ol in participants aged ≥3 years with a	cute respirato	ory tract
20 21 22 23		Patient or population: participants aged ≥3 years with acute respiratory tract infections Intervention: use of ibuprofen Comparison: use of paracetamol			
24 25 26 27 28 29		Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
30 31 32 33		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}
 34 35 36 37 38 39 40 41 42 43 		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			
43 44	392]
45 46 47 48 49 50 51	393 394 395 396 397	Explanations a. Downgraded evidence by 1 level for stu b. Downgraded evidence by 1 level for ind			
52 53 54 55 56 57 58 59 60					
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1 2 3 4	398	Declarations
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7 8 9	400	Not applicable
10 11	401	Consent for publication
12 13 14	402	Not applicable
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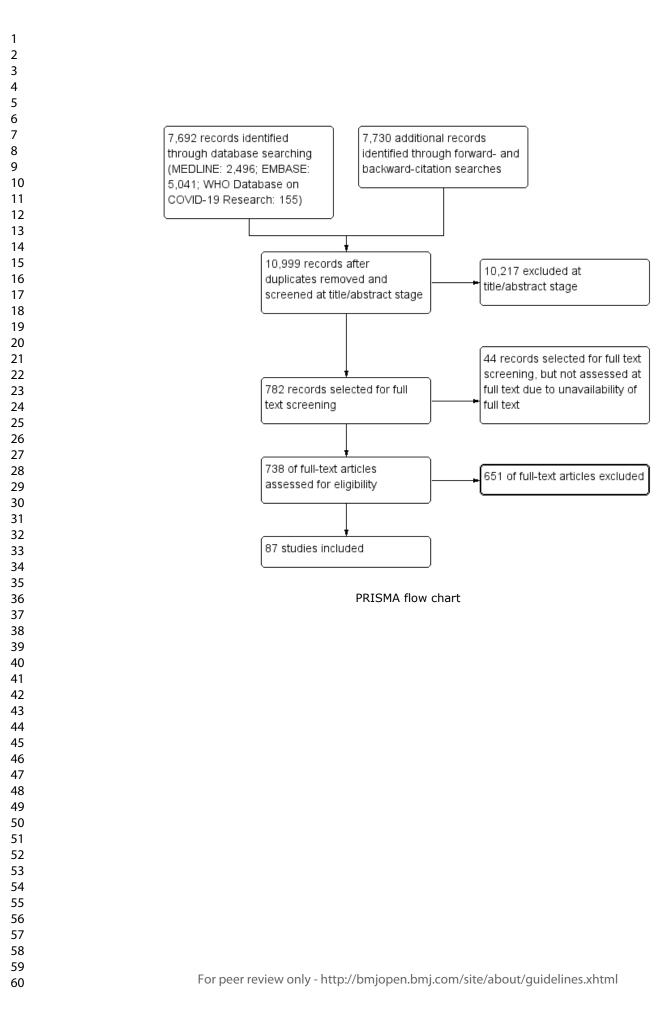
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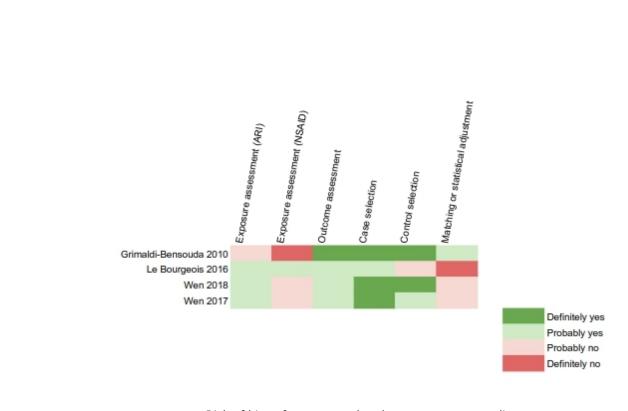
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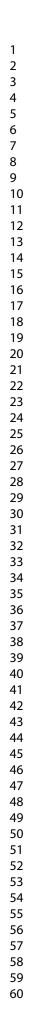


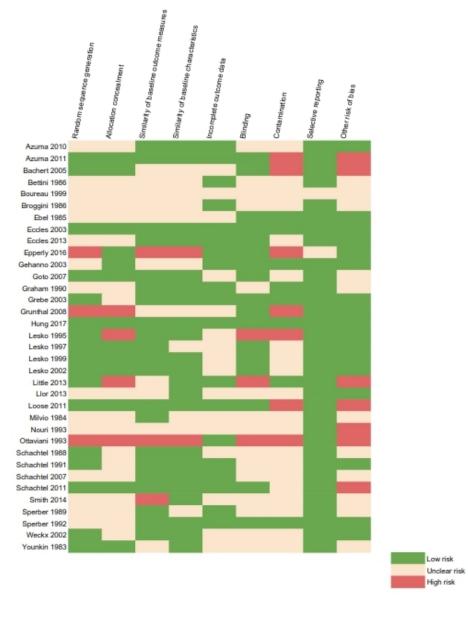
 $\ensuremath{\mathsf{Risk}}$ of bias of case-control and case-crossover studies

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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, Šimon 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 comorbidities (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, we will decide if the number of additional eligible studies identified by the second review author, we will be independently assessed by a second review author.

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.

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Organisational affiliation of the review

> 58 59

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Collaborators

Professor Gerald Gartlehner. Danube University Krems Irma Klerings. Danube University Krems Dr Susan Norris. Department of Information, Evidence and Research, World Health Organization

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; latrogenic 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.

to peer terier only

Versions

24 March 2020

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/	468061
82	80 not 81	3048
83	(english or german).lg.	269973
84	82 and 83	2496

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).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.	1284
39	piroxicam/ or piroxicam.mp.	11670
40	sulindac/ or sulindac.mp.	7587
41	tenoxicam/ or tenoxicam.mp.	2102
42	tolmetin/ or tolmetin.mp.	2688
43	or/1-42	7461
44	coronaviridae/	890
45	coronavirinae/	1047
46	exp coronavirus infection/	1107
47	coronavir*.mp.	18730
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	3594
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	84603
59	(virus or viral).ti,ab.	9262
60	58 and 59	3110
61	exp influenza/	8375
62	(influenza* not (h?em?phil* influenza* or "h influenza*")).mp.	1376
63	flu.ab,ti.	1958
64	(h1n1 or h5n1 or h3n2).mp.	3911
65	or/61-64	1478
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/	2763
71	urti.ti,ab.	1372
72	rhinit*.ti,ab.	39318
73	rhinitis/	18800
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74	pharyngitis/	15196

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

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 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 meloxicam or nabumetone or naproxen or nimesulide or oxaprozin or phenylbutazone or piroxicam or sulindac or tenoxicam or tolmetin or adverse 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:

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- 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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- 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	1	
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	on 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	4
Summary		
Total number of titles/abstracts screened (MEDLINE, EMBASE, Scopus, WHO Covid-19 database)	10999	0
Excluded at title/abstract screening stage	10196	
Included at title/abstract screening stage and assessed at full text	738	1
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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	cteristics o	f studies included in the evider	nce synthesis			miopen-2020-040990 on		
Study ID	Country	Population	Intervention & comparison	Indication for use		Study design	Follow-up	Outcome
Azuma 2010	Japan	<u>N</u> : 170 adults <u>Age range</u> : 20-70 years <u>Mean age</u> : n.r. <u>Disease</u> : Upper respiratory tract infection (URTI)	Zaltoprofen, Placebo	Pain and fever relief	Zaltoprofren 1: 160mg Zaltoprofren 2: 80mg <u>Application</u> : oral <u>Frequency</u> : once	mber 2020. Downlo	6 hours	Counts of Adverse Effects (AEs): Symptoms after administration of study medication
Azuma 2011	Japan	<u>N</u> : 330 adults <u>Mean age</u> : Zaltoprofen: 33 years Loxoprofen: 36 Placebo: 36 <u>Age range</u> : 20-70 years <u>Disease</u> : Febrile URTI	Zaltoprofen, Loxoprofen, Placebo	Pain and fever relief	Dosage: Zaltoprofen: 160 mg	RCT RCT	4 hours	Counts of AEs: Symptoms after administration of study medication
Bachert 2005	Russia	<u>N</u> : 392 adults <u>Age range</u> : 18 - 65 years <u>Mean age</u> : 37.4 years <u>Disease</u> : Febrile URTI	Aspirin, Acetaminophen, Placebo	Pain and fever relief		n. bmi.com/ on April 17.	6 hours	Counts of (severe) AEs
Bettini 1986	Italy	<u>N</u> : 120 adults <u>Age range</u> : n.r. <u>Mean age:</u> 37 years <u>Disease</u> : Influenza-related fever	Diclofenac, Aspirin	Fever relief	2) Aspirin 500 mg Application: oral Frequency:	2024 by quest. Protected	2 days	Count of AEs: Medication side effects
Boureau 1999	France	<u>N</u> : 113 adults Age range: 18-60 years	Ibuprofen, Paracetamol	Symptom relief	Dosage: Ibuprofen: 400mg Paracetamol: 1000mg	cted RCT	48 hours	Counts of AEs: symptoms after

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Study ID	Country	Population	Intervention &	Indication	Medication details	Study	Follow-up	Outcome
		<u>Mean age</u> : n.r. <u>Disease</u> : Tonsillitis	comparison	for use	Application: oral Frequency: once	design		administration of study medication
Broggini 1986	Italy	<u>N</u> : 30 adults <u>Age range</u> : n.r. <u>Mean age</u> : Flurbiprofen 34.4 years; Aspirin 41.6 years <u>Disease</u> : Influenza	Flurbiprofen, aspirin	Symptom relief	<u>Dosage</u> : 1) Flurbiprofen 2) aspirin <u>Application</u> : oral <u>Frequency</u> : twice daily over four	RCT	4 days	Count of AEs: Medication side effects
Ebel 1985	USA	<u>N</u> : 312 adults <u>Age range</u> : 18 - 70 years <u>Mean age</u> : male: 38.5 years female 43.5 <u>Disease</u> : URTI	Sulindac, Placebo	Symptom relief	<u>Dosage</u> : Sulindac 200mg <u>Application</u> : n.r. <u>Frequency</u> : twice per day, 7 days	d from http://bmio	7 days	Counts of (severe AEs
Eccles 2003	Sweden, UK	<u>N</u> : 279 adults <u>Age range</u> : 18-60 years <u>Mean age</u> : IG 25.5 years CG 24.5 years <u>Disease</u> : URTI	Acetylsalicylic Acid, Placebo	Symptom relief	Dosage: 400mg ASA Application: oral <u>Frequency</u> : 1-2 tablets every 4-6 hours for 3 days	RCT	3 days	Counts of AEs: Medication side effects
Eccles 2013	UK	<u>N</u> : 833 participants <u>Age range</u> : n.r. <u>Mean age</u> : n.r. <u>Disease</u> : URTI	Aspirin + Pseudoephedrine, Aspirin, Pseudoephedrine, Placebo	Symptom relief	PSE / S	April 17 20024 by guest	7 days	Counts of AEs
Epperly 2016	USA	<u>N</u> : 683 adults 838 children; <u>Age range</u> : n.r.	NSAIDs, Aspirin, non-use	Improvemen t of the medical	<u>Dosage</u> : n.r. <u>Application</u> : most likely oral intak <u>Frequency</u> : n.r.	Retrospe ctive regi	Adults: 60 days Children: 90	Risk of mortality
		-						27

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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 <u>Disease</u> : pH1N1		course of influenza	Dosage: Diclofenac potassium	based cohort study	days	
Gehanno 2003	France	<u>N</u> : 343 <u>Age range</u> : 20-60 years <u>Mean age</u> : 40 years <u>Disease</u> : Febrile sore throat	Diclofenac potassium, Paracetamol	Pain and fever relief	Dosage: Diclofenac potassium6.25 mg, 12.5 mg and 25 mgParacetamol: 1000 mgApplication: OralFrequency: Once		10 days	Counts of AEs
Goto 2007	Japan	<u>N</u> : 189 <u>Age group</u> : 18-65 years <u>Mean age</u> : Loxoprofen: 29.3 years, Placebo 27.6 years <u>Disease</u> : 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		7 days	Counts of AEs
Graham 1990	Australia	<u>N</u> : 60 adults <u>Age range</u> : 18 - 30 years <u>Mean age</u> : n.r. <u>Disease</u> : 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 Dosage: Diclofenac-K: 12.5mg, multiple, flexible dosing regimen		28 days	Counts of AEs: Symptoms after administration o study medication
Grebe 2003	Germany	<u>N</u> : 356 adults <u>Age range</u> : ≥ 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		multiple, flexible dosing regimen <u>Application</u> : oral <u>Frequency</u> : 3 days			
Grimaldi- Bensouda 2010	France	<u>N</u> : 177 children <u>Age range</u> : 2 months - 16 years <u>Mean age</u> : n.r. <u>Disease</u> : Fever, pain, rheumatic indication	Ibuprofen, Aspirin, non-use	Relief of fever		Case- cross- over study	7 days	Risk of upper gastrointestinal bleeding
Grunthal 2008	Germany	<u>N</u> : 2341 <u>Age range</u> : n.r. <u>Mean age</u> : ca. 40 years <u>Disease</u> : 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) <u>Application</u> : oral <u>Frequency</u> : 1) mean: 1.6 doses 2) mean: 1.9 doses	3	3 days	Counts of AEs
Hung 2017	Hong Kong	<u>N</u> : 217 adults <u>Age range</u> :_≥ 18 years <u>Median</u> : 80 years <u>Disease</u> : 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 <u>Application</u> : oral <u>Frequency</u> :		30 days	Risk for Mortality (at 30 / 90 days), duration of hospitalization
								29

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					2020-040			
Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details		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	<u>N</u> : 166 children <u>Age range</u> : 3 -15 years <u>Mean age</u> : Cases: 4.1 ± 2.3 Controls: 3.8 ± 2.3 <u>Disease</u> : 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	study	Cases and controls: 15 days (retrospectiv e)	Risk of hospitalization (empyema)
Lesko 1995	USA	<u>N</u> : 83,915 children <u>Age range</u> : 6 months - 12 years <u>Mean age</u> : n.r. <u>Disease</u> : Febrile illness	Ibuprofen, Paracetamol	Relief of symptoms of febrile illness	Dosage: Ibuprofen 1: 5mg/kg Ibuprofen 2: 10mg/kg Paracetamol: 10 mg/kg <u>Application</u> : oral <u>Frequency</u> : Ibuprofen 1 and 2: median number of doses 6-10, median duration 3 days		4 weeks	Risk of hospitalization fo acute gastrointestinal bleeding, acute renal failure, anaphyla xis or Reye's syndrome Counts of other (severe) AEs leading to hospitalization
Lesko 1997	USA	<u>N</u> : 288 children <u>Age range</u> : 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	20-040990 Study 01 desig		Outcome
		<u>Mean age</u> : n.r. <u>Disease</u> : Febrile illness		febrile illness	Acetaminophen: 12mg/kg <u>Application</u> : oral <u>Frequency</u> : All: median number of doses 7, median duration 2 days	19 November 2020		
Lesko 1999	USA	<u>N</u> : 27,065 children <u>Age range</u> : 1 - 23 months <u>Mean age</u> : n.r. <u>Disease</u> : Febrile illness	Ibuprofen, Acetaminophen	Relief of symptoms of febrile illness	Dosage: Ibuprofen 1: 5mg/kg Ibuprofen 2: 10mg/kg Acetaminophen: 12mg/kg <u>Application</u> : oral <u>Frequency</u> : All: median number of doses 6-10 median duration 3 days	RCT ROwnloaded from http://bmiopen.bmi.com/ o	4 weeks	Risk of hospitalization for acute gastrointestinal bleeding, acute renal failure, anaphyla xis or Reye's syndrome Counts of other (severe) AEs leading to hospitalization
Lesko 2002	USA	<u>N</u> : 1879 children <u>Age range</u> : 6 months - 12 years <u>Mean age</u> : n.r. <u>Disease</u> : Febrile illness	Ibuprofen, Acetaminophen	Relief of symptoms of febrile illness	Dosage: Ibuprofen 1: 5mg/kg Ibuprofen 2: 10mg/kg Acetaminophen: 12mg/kg	April 17. 2024 by	4 weeks	Risk of outpatient visits or hospitalization for asthma
Little 2013	UK	<u>N</u> : 89 children and adults <u>Age range</u> : ≥ 3 years <u>Mean age</u> : Ibuprofen 34; Paracetamol 34; Both 33 <u>Disease</u> : 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 RCT Protected by	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	990 on 1	Study design	Follow-up	Outcome
		(upper and lower)				9 Nov			intervention
Llor 2013	Spain	<u>N</u> : 416 <u>Age range</u> : 18-70 years <u>Mean age</u> : 45.1 years <u>Disease</u> : RTI	Ibuprofen, Amoxicillin- clavulanic acid, Placebo	Symptom relief	<u>Dosage</u> : Ibuprofen: 600 mg Amoxicillin-clavulanic acid: 500 mg <u>Application</u> : n.r. <u>Frequency</u> : 3 daily for 10 days	November 2020. Dow	RCT	11-13 days	Counts of AEs: events possible related to drug
Loose 2011	Germany	<u>N</u> : 640 adults <u>Age range</u> : not reported <u>Mean age</u> : 19.6 years <u>Disease</u> : 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 <u>Application</u> : oral <u>Frequency</u> : once	nloaded from http://bmjo	RCT	6 h	Counts of AEs
Milvio 1984	Switzerlan d	<u>N</u> : 50 adults <u>Age range</u> : n.r. <u>Mean age</u> : Nimesulide: 38 years; Benzydamine: 49 years <u>Disease</u> : Inflammation of the ear, nose and throat	Nimesulide, Benzydamine	Treatment of fever and inflammatio n	Dosage:1) Nimsulide 100 mg 2) Benzydamine 75 mg <u>Application</u> : oral <u>Frequency</u> : twice a day for 10 days	pen.bmj.com/ on Apri	RCT	10 days	Count of AEs: Medication sid effects
Nouri 1993	Austria or Switzerlan d	<u>N</u> : 65 adults <u>Age range</u> : 35-62 years <u>Mean age</u> : IG: 39 years CG: 53 years <u>Disease</u> : Non-bacterial inflammation of the ear, nose and throat	Nimesulide, Naproxen	Treatment of inflammatio n	<u>Dosage</u> : 1) Nimseluide 100 mg 2) Naproxen 500 mg <u>Application</u> : oral <u>Frequency</u> : Twice daily, mean duration 8.7 days	117, 2024 by guest. Prot	RCT	10 days	Counts of AEs

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Study ID	Country	Population	Intervention & comparison	Indication for use		Study design	Follow-up	Outcome
Ottaviani 1993	Italy	<u>N</u> : 940 children and adults <u>Age range</u> : 15-77 years <u>Mean age</u> : 38 years <u>Disease</u> : URTI or Otitis media	Nimesulide	Symptom relief	$\frac{Application}{Frequency}$: twice a day for or a mean (+ SD) of 10 (+ 4) days	Cohort study	10 days	Counts of AEs
Schachtel 1988	USA	<u>N</u> : 120 adults <u>Age range</u> : 18 - 88 years <u>Mean age:</u> Ibuprofen: 41.5 years, Acetaminophen: 46.1 <u>Disease</u> : Severe throat pain	Ibuprofen, Acetaminophen, Placebo	Symptom relief	· ·	RCT	1 day	Counts of AEs
Schachtel 1991	USA	<u>N</u> : 210 adults <u>Age range</u> : 18 - 83 years <u>Mean age</u> : 30 <u>Disease</u> : Tonsillopharyngitis/URTI	Aspirin + caffeine, Aspirin, Placebo	Pain relief	<u>Dosage</u> : Aspirin 1: 800mg + 64mg Aspirin 2: 800mg Placebo <u>Application</u> : oral <u>Frequency</u> : Once		2 hours	Counts of AEs
Schachtel 2007	USA	<u>N</u> : 197 adults <u>Age range</u> : ≥ 18 years <u>Mean age</u> : n.r. <u>Disease</u> :_Tonsillopharyngitis	Valdecoxib, Placebo	Symptom relief	Dosage: Valdecoxib 1: 40 mg Valdecoxib 2: 20 mg Placebo <u>Application</u> : n.r. <u>Frequency</u> : once	RCT	24 hours	Counts of AEs
Schachtel 2011	USA	<u>N</u> : 269 adults <u>Age range</u> : 18 - 30 <u>Mean age</u> : 19 <u>Disease</u> : Sore throat	Celecoxib, Placebo	Pain relief	Celecoxib 1: 50-mg + 50 mg after 5 6-12 hours Celecoxib 2: 100-mg + placebo after 6-12 hours Celecoxib 3: 100-mg + 50 mg after 6 12 hours		24 hours	Counts of AEs
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					Medication details			
Study ID	Country	Population	Intervention & comparison	Indication for use	S S S S S S S S S S S S S S S S S S S	design	Follow-up	Outcome
					6-12 hours Zong Constraints Co			
Smith 2014	USA	<u>N</u> : 207 adults <u>Age range</u> : 18 - 34 years <u>Mean age</u> : 21 years <u>Disease</u> : URTI	Ibuprofen + Caffeine, Ibuprofen, Caffeine, Placebo	Symptom relief	Dosage:Ibuprofen + Caffeine:No200mg + 100mgIbuprofen:200mgCaffeine:100mgPlaceboApplication:OralFrequency:once		3 hours	Counts of AEs
Sperber 1989	USA	<u>N</u> : 58 adults <u>Age range</u> : n.r. <u>Mean age</u> : 20-21 years <u>Disease</u> : Cold	Ibuprofen + Pseudoephedrine, Pseudoephedrine Placebo	Symptom relief	Dosage: Pseudoephidrine + Ibuprofen: 60mg + 200mg Pseudoephidrine 60mg Placebo Application: Oral Frequency: 2 doses the first day, 60 doses over next 4 days		14 days	Counts of AEs: symptoms after administration o study medicatio
Sperber 1992	USA	<u>N</u> : 87 adults <u>Age range</u> : n.r <u>Mean age</u> : 21.4 years <u>Disease</u> : Cold	Naproxen, Placebo	Symptom relief	Dosage: See below Application: oral <u>Application</u> : oral 11 <u>Frequency:</u> 7 Naproxen 1: 1 loading dose 20 (400mg) + 3 times daily 200mg for 5 5 days 20 Naproxen 2 and 3: 1 loading dose 20 (500mg) + 3 times daily 500mg for 3	RCT	5 days	Counts of AEs
Wen 2017	Taiwan	<u>N</u> : 9,793 adults <u>Age range</u> : >20 years	NSAID, No NSAID	Pain and fever relief	5 days of other second	Case- Crossove	Cases: 7 days	Risk of myocard 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			<u>Frequency</u> : n.r.	Rovember		
Wen 2018	Taiwan	<u>N</u> : 29,518 adults <u>Age range</u> : > 20 years <u>Mean age</u> : 73.4 years <u>Disease</u> : Acute respiratory infection (ARI)	NSAID (any single-active-ingre dient NSAIDs, non-use	Pain and fever relief	Frequency: n.r.	Case- Crossove r Study	Cases: 7 days	Risk for ischemic and hemorrhagic stroke
Weckx 2002	Brazil, Colombia and Mexico	<u>N</u> : 357 adults <u>Age range</u> : ≥ 18 years <u>Mean age</u> : Celecoxib once daily: 32 Celecoxib twice daily: 31 Diclofenac: 32 <u>Disease</u> : Viral pharyngitis	Celecoxib, Diclofenac	Symptom relief	Dosage: 1) Celecoxib 200 mg 2) Diclofenac 75 mg Application: oral	aded from http://bmioper	5 days	Counts of (serious) AEs
Younkin 1983	USA	<u>N</u> : 47 children and adults <u>Age range</u> : 17-20 years <u>Mean age</u> : n.r. <u>Disease</u> : Influenza	Aspirin, Amantadine		Application: Oral <u>Frequency:</u> For 5 days Aspirin: 10 daily Amantadine 1: 1 daily	RCT	7 days	Count of AEs: Medication side effects

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

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10. Effects	s on primary outco	mes reported by s	tudies included in the evide	
Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
Comparison	of NSAID use with no	NSAID use: Effects on	mortality	- mber 20
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 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 adult with H1N1 influenza are unclear. The confidence interval of the effect estimated is large, and includes the possibility of positive, null or negative effect.
NSAID use v	s. no NSAID use: Effec	ts cardiovascular ever	its	mjope
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 associate with a higher odds ratio for ischemic streate 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 wi ARI on risk for ischemic stroke is unclear.
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		_		Narrative description				
Study ID	Intervention and control	Outcome	Effect estimate	Narrative description				
			= 1	possibility of a positive, null or negative	ffect.			
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 rewith a higher odds ratio for hemorrhagication individuals with an ARI not expose b) individuals without an ARI expose c) individuals without an ARI not expose c) individuals without an ARI not expose ARI on risk for hemorrhagic stroke is use the possibility of a positive, null or negative for the possibility of a positive, null or negative for the possibility of a positive, null or negative for the possibility of a positive, null or negative for the possibility of a positive, null or negative for the possibility of a positive, null or negative for the possibility of a positive for the possibility of a po	stroke compared to: ed to NSAIDs, ed to NSAIDs, posed to NSAIDs. hat the effect of NSAID in patients with clear. The confidence intervals includ			
Multiple cor	mparisons: Effects on	adverse event counts						
Multiple cor Azuma 2010	nparisons: Effects on Zaltoprofen vs zaltoprofen vs placebo	adverse event counts Counts of severe adverse events (SAEs)		That study reports several mild adverse severse adverse events occured (Quote 2 joint pain cases occurred in the 80-mg muscle pain, 1 glutamic oxaloacetic tran dehydrogenase (LDH) increase occurred were mild.")	e events, and explicitly states that r "Three headaches, 2 odynophagias ar group. One odynophagia, 1 joint pain, isaminase (GOT) increase and 1 lacta			

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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 sevents 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 were recorded in one patient treated with Aspirina and in five patients tre with Aspirin. No patient had to discontinue the treatment because of effects."
Boureau 1999	lbuprofen vs Paracetamol	Counts of SAEs	Not explicitly reported	The study reports that "[t]here were no serious adverse effects and statistically significant difference in the incidence of adverse events in the treatment groups", but provides only very little detail on whether and how 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 AS dyspepsia necessitating withdrawal of treatment and 1 bitter taste) and 3 c 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 $\frac{2}{3}$ verse experiences reported was r 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 series 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 feeting were not related to the study drug."
Gehanno 2003	Diclofenac potassium vs Paracetamol	Counts of SAEs	Diclofenac potassium 6.25 mg: O SAEs Diclofenac potassium 12.5mg: O SAEs Diclofenac potassium 25 mg: O SAEs Paracteamol: O 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 deates during the trial."
Goto 2007	Loxoprofen vs placebo	Counts of SAEs	Not explicitly reported	The study reports that "[e]ight patignts 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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106			BMJ C	ipen Contraction C	
Study ID	Intervention and	Outcome	Effect estimate	Narrative description	
	control				2
Grunthal 2008	Acetylsalicylate (aspirin) + pseudoephedrin vs paracetamol + caffeine + chlorphenamine + vitamin C	Counts of SAEs	Not explicitly reported	The study reports that 4.8% of participe participants receiving aspirin reported sid moderate severity". The most common "gastric pain, upper abdominal pain and r	e effects, which were "mostly of mil side effects in the aspirin group v
Hung 2017	Clarithromycin + naproxen + oseltamivir vs oseltamivir	Counts of SAEs	Not explicitly reported	The study notes that "no patient in our drug-drug interaction." The study does 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 congroup than in the Ibuprofen or placeboar study, a digestive haemmorrhage require occurred in the amoxicillin-clavulanic acid	groups. The only SAE in recorded in ng admission to the intensive care
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 (17.5 %) patients were reported or ob- serious. "	Served. All of these events were
Milvio 1984	Nimesulide vs benzydamine	Counts of SAEs	Not explicitly reported	The study reports that "[n]imesulide was patient suffered from moderate gastric p	
Nouri 1993	Nimesulide vs	Counts of SAEs	Not explicitly reported	The study notes that "[t]herapy with nig	

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Study ID	Intervention and control	Outcome	Effect estimate	Narrative description	090 on 1
	Naproxen			associated with adverse reactions. In the experienced episodic gastralgia of mode and the other on the eighth day of the modified by either treatment."	ate intensity, one starting on the third
Ottaviani 1993	Nimesulide	Counts of SAEs	Nimesulide: 10 SAEs out of 940 patients	The study reports that "[t]he drug was v reported adverse effects, only 26 had Physicians' assessments of therapeutic were good in most patients". The SA sweating, flush, loss of appetite, vision dyspepsia, nausea, () [v]ertigo, () [r]a	of be withdrawn from treatment. (Deficacy and tolerability of treatmen Preported included "[w]ater retention 戳isturbance, () [h]eartburn, gastralgia
Schachtel 1988	Ibuprofen vs acetaminophen (paracetamol) vs placebo	Counts of AEs	Not explicitly reported	The study reports that "[n]o adverse e The study provides only very little o monitored.	
Schachtel 1991	Aspirin vs placebo	Counts of SAEs	Not explicitly reported	The study reports that "[o]f the 210 part (receiving aspirin) was discontinued aff (nausea and vomiting) (). There were the trial."	er 1 hour because of an adverse effec
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 discontinued the study as a result of an a	
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 due to an AE. Overall, the incidence of	ညှိerious AEs, deaths, or discontinuation
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106			BMJ C	miopen-2020-0	
Study ID	Intervention and control	Outcome	Effect estimate		2020-040990 on 1
			Celecoxib (low dose) + Placebo: 0 SAEs Placebo: 0 SAEs		9 Novembe
Smith 2014	Ibuprofen + caffeine vs ibuprofen vs caffeine vs placebo	Counts of SAEs	Not explicitly reported	The study reports that "[t]here were n studymedication was well tolerated."	e serious adverse events reported, an
Sperber 1989	Pseudoephidrine + ibuprofen vs pseudoephidrine vs placebo	Count of SAEs	Not explicitly reported	The study notes that both drugs "were withdrew from the study due to advers following "possible adverse effects of sleeping, Lethargy, Indigestion".	drug effects." The study mentions th
Sperber 1992	Naproxen vs placebo	Counts of SAEs	Not explicitly reported	The study reports that "[s]ide effects to three cohorts. One volunteer in the nap symptoms after two doses of the drug, treatment without incident. Two gastrointestinal complaints."	exen group experienced gastrointesting but after missing two doses, complete
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." Pril 17 2024 b
Younkin 1983	Apsirin vs amantadine (1x daily) vs amantadine (2x daily)	Counts of SAEs	Not explicitly reported	The study reports that "[a] number of symptomatic complaint on at least on medication. In the aspirin treatment gro did not take all prescribed capsules. All days of the study. Six patients also had a or tinnitus."	ccasion that they attributed to th pup, the subjects took all tablets, but si bubjects took all medications the first least one episode of insomnia, nauses

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Study ID	Intervention and control	Outcome	Effect estimate	Narrative des	scription	0990 on 1		
Comparison	of ibuprofen with ace	etaminophen (paraceta	amol): Effects on the rate of reco	nsultations		9 Nover		
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)	complications paracetamol the combine ibuprofen vs. 0.012). The s not serious,	come reconsultation s within one month), t group, 58/295 (20%) in d ibuprofen/paracetar the paracetamol grou tudy reports that "[m] and three could be record form."	he study rep n the ibupro nol group. up vess 1.67 ost of the 17	orts 35/300 (11%) e fen group and 48/28 The adjusted risk ra (95% CI: 1.12 to 2. 7 "complications" rec	vents in the 85 (17%) for atio for the 38; p-value: corded were
11. Characte	eristics of and outcom	es reported in studies	included in the evidence mapping					

Study ID	Study title	Study design	Partici- pants	Follow up	Drugs	Disease / pathogen	Adverse outcome	Reporting on adverse outcomes
			(n)				reporting	
Aksoylar	Evaluation of sponging and	RCT	224	3 hours	Sponging alone	URTI, Pneumonia,	Thế study	"No serious side effects were
1997	antipyretic medication to				VS.	Otitis media,	explicitly	observed that required stopping
	reduce body temperature in				Sponging with a	gastroenteritis, UTI,		the treatment."
	febrile children				single oral dose of	Others	that there	
					aspirin 15 mg/kg,		weite no	
					or paracetamol 15		severe	
					mg/kg, or		adværse	
					ibuprofen 8		outcomes;	
					mg/kg		rot	
							ected by	
							copyrigh	43

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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	Additional and a study of the study expericitly reports on miles or moderate adverse outeromes, but to the study does not to the study of the study	"Of the 348 patients inclu 14 patients experienced adverse effects. [] In ibuprofen group, 9 pat reported 13 adverse effect of which was experie twice. In the paracet group, one child had adverse effect and in the as group four patients had 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 expandicitly reparts severe adverse outcomes; 	"All adverse events report were either mild or moderal severity. One serious addrevent was reported in a para after having taken seven of of randomized treat (paracetamol) on the first The child was suffering persistence of wavering and onset of cough – an revealed pneumopathy. child recovered 4 days late withdrew from the trial. event was recorded as he no relationship to study dru
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)	explicitly	"Gastrointestinal ad- events were observed in patients (3 treated nimesulide and 8 treated lysine-aspirin), but required withdrawal therapy. In addition,
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							o- o- 0-40 920 megtion severe adværse out≹omes;	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	They study expectly reports on mile 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 expective reports that there were no adverse outcomes (without specifying the severity);	"There were no relevant adverse effects observed during treatment or significant changes in the haematological profile in any patient."	
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f 106					BMJ Open			mjopen-2020-0409g0 Theory	
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 Dexibuprofen	vs.	Fever due to URTI	Theo study expicitly reports that there weee no severe adverse outcomes;	"A total of 84 adverse event 64/263 patients were report Adverse events inclu vomiting, diarrhea, abdom pain, constipation, ra elevated liver enzyme, thrombocytopenia. [] Th were no serious adverse event in which the patient(s) had b exposed to a danger to required a longer hospital s or had acquired permanent major sequalae."
Erlewyn- Lajeunesse 2006	Randomised controlled trial of combined paracetamol and ibuprofen for fever	RCT	123	1hour	Paracetamol Ibuprofen vs. Both	vs.	Fever	The study expanding study reparts on mile or moderate adverse outcomes, bug does not meetion severe adverse outcomes;	One child experienced a ra temperature drop from 39 to 37.7°C in one hour. She admitted for observation recovered spontaneously. " child in the paracetamol gr received a dose of 27.8 mg in error. The child did not su any adverse consequences f this overdose. There were 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 Paracetamol	+ vs.	Fever due to: Upper RTI, Lower RTI, Gastrointestinal infection, Upper UTI, Soft tissue Infection, Otitis, Other	The study expective reports that there	
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							020-040	
							mjopen-2020-040990 on 19 Nove	neutropenia prior to the fi intake of paracetamol and t was consequently considered unrelated to the stu 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 outeomes;	"A total of 18.4% (21/114) subjects reported 1 or mo adverse events; none we classified as serious. [] Dru related adverse events, that those that were classified by t investigator as definite probably, possibly, or unknown relationship to stu drug, were reported by 13.2 (15/114) of subjects (data r provided). All but 1 adver event (cough increased) w 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 thet severity);	"No adverse reactio abnormal physical findings abnormal laboratory resu attributable to eit nimesulide or paracetar 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 mile or moderate adverse	"Adverse reactions were seer the form of epigastric pain a vomiting in one patient nimesulide group and th patients in paracetamol group
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							outcomes, buto does not 3 mextion severe adverse outgomes;	
Hadas 2011	Premarketing Surveillance of Ibuprofen Suppositories in Febrile Children	Safety study, uncontrolled	490	7 days	Ibuprofen suppositories	Fever	The study explicitly reports on mile or moderate adverse outcomes, but does not mention severe adverse outcomes;	"Adverse reactions reported in 8 patients (1 95% confidence interval = 3.25). The most co adverse event was diarri children (0.8%, 95% confi interval = 0.24-2.2) had dia immediately after administration of the drug children developed a ra child had shivering, and 2 had rectal burning 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 exports reports severe adv rse out 17, 2024 by guest. Protected by	Parents recorded and effects. "The most co adverse effects were diand and vomiting, which equally distributed be groups. The overall num children experiencing and events was, however, too to make mean comparisons be treatments. Five children admitted to he (constituting serious and events)": PCM group ibuprofen group: 3, PCN 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	lbuprofen vs. Acetaminophen	Fever	Theo study explicitly reports on mile or moderate adverse outeomes, but does not metion severe adverse outeomes;	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
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 expanding study reparts that there were no adverse outcomes (without specifying their severity);	"In this single-dose study no side-effects were observed with either drug."
						<i>^/</i>	April 17, 2024 by guest. Protected by copyright.	
		For peer 1	review onl	y - http://br	njopen.bmj.com/site/a	about/guidelines.xhtm	l by copyright. 	49

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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)	exponential reports that there wee no adverse outeomes (without specifying they severity);	"No adverse reaction abnormal physical findings, abnormal laboratory rest attributable to either ibupro or acetaminophen wo 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	d Theomore study expansion of the study reparts severe advised on the study output of	"Adverse events were repo for 54 of the 100 patients, most (97%) being classified mild to moderate in seve [] There were no de reported in this study. Th were four (4%) subjects whom six serious adv events were reported. In intravenous ibuprofen gro two subjects experienced serious adverse events; with pancreatitis and hepa and one with cardiac arrest pneumothorax. In acetaminophen group, two subjects experienced serious adverse events; ple effusion, and intra-abdom abscess. None of the ser adverse events were deel related to either intraver ibuprofen or acetaminophe the opinion of an independ

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							-040990 on 19 November 2020. Downloaded fro	data safety monitor."
Kim 2013	Dexibuprofen for fever in	RCT	260	4 hours	Dexibuprofen	URTI	The study	"There were no significar
	children with upper respiratory tract infection				(two different doses) vs. Ibuprofen		expericitly reports that there were adverse outeomes; on April 17, 2024 by gu	differences in number of A experienced (P = 0.98), no were there differences in number of patient experiencing AE in each group (DEX 1, n = 33; DEX 2, n = 34 control, n = 35). When AE were classified according to severit (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 an 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 mile or moderate adverse	"During the study period, (21%) of all patients had symptoms includir diarrhea, flatulence, emesi decreased appetite, epigastr pain, nausea, headache, ar
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							mention severe adværse outgomes;	insomnia. These symptom not prevent any of the pat from taking the medications. There were differences between grou the incidence of any of 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 mile or moderate adverse outcomes, but does not mettion severe adverse outcomes;	"As far as the monitorir other ADR was concerned, a few adverse effects nar epigastric pain, vomiting encountered and on comp it in different groups, marked difference was four
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 mile or moderate adverse outcomes, but does not mention severe adverse outcomes;	"One patient devel hypothermia 4 h follo injection of diclofenac sodiu "no asthmatic attacks occu in the emergency room d the observation" "Two patients with a histo asthmatic bronchitis wheezing" "there were no reported al 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,	0 '0 '	"No obvious toxicities observed" "Asthma": 2/157 in ibup
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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)	mjopen-2020-040900 or moderate adverse outeomes, bute does note tion severse adverse adverse	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	outeomes; The study experts on mile or moderate adverse outcomes, but does note 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 experies, reperts severe adverse outcomes; y guest. Protected by copyright	"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	mjopen-2020-040990 on 19 Noveml	adverse events during study: 10/76 patients (13 the ibuprofen group ha events and 14/74 pa (19%) in the paracetamol 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	lbuprofen + acetaminophen vs. lbuprofen + placebo	Febrile illness	The study expected reports that there we e no severe adverse outgomes;	"No serious adverse rea were observed in subjects. In addition, no the subjects developed symptom or sign suggest gastrointestinal, hepation 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, Otitis, Pharyngitis, Otitis, Tracheitis, Bronchitis, Exanthema	The study experts on mile or moderate adverse outgomes, buto does not mention severe adverse outgomes, buto does not mention	"Three patients treated nimesulide and 6 pa treated with parace withdrew from therapy be of urticaria, vomiting 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	lbuprofen vs. Dipyrone (two different doses)	URI and LRI	The study explicitly reports on mile or moderate adverse outgomes, butg does not	"There was only one ca mild, transient urticaria, appeared 30 minutes afte ibuprofen administration girl aged 9.1 months. [urticaria remitted by the t reaching three hours ibuprofen administ without any specific thera

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							meotion severe adverse outeomes;	
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 expective reports that there were no severe adverse outcomes; de	"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 experts on mile or moderate adverse outsomes, but does not mention severe adverse outsomes;	"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 exponential reports they 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	weige no severe adverse outgomes; overmber 2020. Download Thee study	enzymes and renal fin were observed in 8 chi (1.7%) and 14 children (3 respectively, but none o acute-stage labor abnormalities persisted to 14-day follow-up evalue and there were no statist significant differences a the groups (P=.60 for abno liver function and P=.93 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 expectively reports on mile or moderate adverse outeomes, but does note megtion severe adverse outeomes;	"In the present study only patient had an allergy fav urticaria in the ketop 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 outgomes st. Protection The study	"No significant between- differences were observed respect to adverse even serious adverse events. serious adverse events occ in the acetaminophen g and 12 in the ibuprofen g No deaths from any 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	expolicitly	"No side effects from the were seen in this serie
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					BMJ Open		mjopen-2020-040 rep o rts	
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					Aspirin vs. Paracetamol vs. Aminophenazone	infection	reports that there were no adverse out omes (without spectifying the 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 the 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 expected reports that there wee no adverse outcomes (without specifying their severity);	"Paracetamol, ibuprofen an nimesulide were remarkabl well tolerated and there wer no drug-related side effect recorded, includin haematological abnormalitie 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 mile or moderate	"Fourteen adverse events wer recorded in nine patient [Ibuprofen treatment: acetaminophen treatment:] The other adverse even
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f 106					BMJ Open		1jopen-	
							mjopen-2020-0409erse	
							but does not mention severe adverse outcomes;	(ibuprofen), and hypother [ibuprofen: 2, acetaminop 1]."
Vauzelle- Kervroedan 1996	Antipyretic efficacy of tiaprofenic acid in febrile children	RCT	55	48 hours	Tiaprofenic acid vs. Placebo	Fever	The study experience of the study reports on mile or moderate adværse outsomes, but does not mention severe adværse outsomes;	
Vauzelle- Kervroedan 1997	Equivalent antipyretic activity of ibuprofen and paracetamol in febrile children	RCT	116	2-4 days	lbuprofen vs. Acetaminophen	Fever	The study explicitly reports on mile or moderate adverse outcomes, buth does not mention severe adverse outcomes;	"Two children vomited du the study (1.7%), both of w 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 expericitly	"No serious or severe adv events were noted in any of
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					BMJ Open		mjopen-2020-040 reports	F
	iburgha and parastruct				Combination		0 0 40 9 9 1	answer []] in the investor
	ibuprofen and paracetamol- ibuprofen combination for treatment of febrile children				Combination	respiratory infection, viral illness, bronchiolitis	reports that there were no severe adverse outgomes; 2020. Downloaded from http://bmjop	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 expected reports that there well 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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Page 97 of	106				BMJ Open	
1 2						
3 4 5 6 7 8 9						
10 11 12 13 14 15 16 17	Walson 1992	Comparison of Multidose Ibuprofen and Acetaminophen Therapy ir Febrile Children	64	48 hours	Ibuprofen vs. Acetaminophen	Fever

f 106					BMJ Open		mjopen-2020-0409900 does	
							outgomes, buto does not 1 mention severe adværse outgomes;	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	Theory study expficitly reports that there weare adværse outgomes;	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 expected of the study reports on mile or moderate adverse outeomes, but does not to mention severe adverse outeomes;	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 expondicitly repopirts on mile or	"Most of the adverse events were gastrointestinal in nature, such as vomiting and diarrhea. Of the total adverse events
		For poor v		, http://bm	ionon hmi com (sito (about/quidelines xhtm	copyright.	60

Yilmaz 2003Intramuscular Dipyrone Versus Oral Ibuprofen or Nimesulide for Reduction of SettingRCT252 S2 hoursIbuprofen vs. Ibuprofen vs. Nimesulide, dipyroneFeverThe settingThere were no statistic settingYoon 2008The effects and safety of dexibuprofen compared with ibuprofen ibuprofen compared with ibuprofen compared with ibuprofen compared with ibuprofen ibuprofen compared with ibuprofen compared with ibuprofen ibuprofen compared with ibuprofen ibuprofen compared with ibuprofen compare						BMJ Open		mjopen-2020-040 moderate	
Yilmaz 2003Intramuscular versus Oral Ibuprofen or Nimesulide for Reduction of 								outcomes, butz does not meation severe adverse outcomes;	considered drug-relate comprised 17% of the dipyrom 15% of the acetaminophen, an 27 % of the ibuprofen group There were no statistical significant differences amor the three groups with respect to the incidence of adverse
Yoon 2008The effects and safety of dexibuprofen compared with ibuprofen in febrile children caused by upper respiratory tract infectionRCT2553 daysDexibuprofen (two different doses) IbuprofenFever due to URTIThe study expective mildright moderate level were report in 32 children (12.7%) du moderate level were report ibuprofenThe study expective mildright moderate level were report in 32 children (12.7%) du moderate level were report ibuprofenYoon 2008The effects and safety of dexibuprofen compared with ibuprofen in febrile children tract infectionRCT2553 daysDexibuprofen (two different doses)Fever due to URTIThe study expective moderate level were report in 32 children (12.7%) du moderate level were report in 32 children (12.7%) du moderate level were report in 32 children (12.7%) du moderate level were report adverse outcomes, but does abdominal pain, decreased note		versus Oral Ibuprofen or Nimesulide for Reduction of Fever in the Outpatient	RCT	252	2 hours	Nimesulide,	Fever	The study expanding study reports on mile or moderate adverse outcomes, but does not mention severe adverse	"An erythematous eruptic occurred in only one mpatien who used nimesulide. Th number of cases where th axillary temperature dropped below 36°C was 15 (17.9%) the diphyrone group, six (7.1%) in the ibuprofen group, ar three (3.6%) in the nimesulic
adværse thrombocytopenia" outæomes;	Yoon 2008	dexibuprofen compared with ibuprofen in febrile children caused by upper respiratory	RCT	255	3 days	(two different doses) vs.		The study expective reperts on mild or moderate adverse outcomes, but does not mention severe adverse	oedema, skin rash, elevate liver enzyme level ar

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Page 99 of	106					BMJ Open		mjopen-:	
1 2 3 4	Yoshikawa 2001	Study of Influenza-Associated Encephalitis/Encephalopathy	Case series	20	Through	Diclofenac sodium,	Influenza	mjopen-2020-04098 Theo study expansion	Only children with influenza- associated
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24		in Children During the 1997 to 2001 Influenza Seasons			course	acetaminophen, a combination of sulpyrine and acetaminophen, combination of acetaminophen and Mefenamic acid		reports severe adverse outber 2020. Downloaded from http://bmjopen.bmj.cc	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
25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42							0n/	com/ on April 17, 2024 by guest. Protected by copyright.	acetaminophen)." 62
43 44			For peer r	eview only	/ - http://bm	ijopen.bmj.com/site/a	about/guidelines.xhtm	. 	

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".							

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).

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)	⊕⊕⊕⊕ нісн
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 ♭
Hospitalization for acute renal failure, anaphylaxis Follow-up: 4 weeks	Lesko 1995 O events in either group	83915 (1 RCT)	⊕⊕⊕⊕ нісн
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 ♭
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 ♭
*Calculations for this	s estimate were done by the review authors.		
High certainty: We a Moderate certainty: estimate of the effect	up grades of evidence re very confident that the true effect lies close to that of the estima We are moderately confident in the effect estimate: The true effect t, but there is a possibility that it is substantially different onfidence in the effect estimate is limited: The true effect may be s ffect	t is likely to be ubstantially dif	close to the ferent from

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: concerns for incomplete outcome reporting.
- b. Downgraded evidence by 1 level for imprecision. tor peer teriew only

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

 $\label{eq:comparison: No use of NSAIDs} \textbf{Comparison: No use of NSAIDs}$

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-pare	nteral 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	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)	
exposure of patients 365d before the event			
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)	
3. Low dose non-paren	teral 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)	
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
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)	
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)	

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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)	
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)	
7. Coxibs	0		
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 LC
8. NSAIDs other than C	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)	
9. More than one NSAI	Ds	7	
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)	
Moderate certainty: We are r possibility that it is substantiall Low certainty: Our confidenc	confident that the true effect lies close to that of the estimate of the effect noderately confident in the effect estimate: The true effect is likely to be close to the estin	stimate of the effe	ect

Explanations

¹All 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. ²All 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 to beet terien only negative effects.

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PRISMA 2009 Checklist

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PRISMA 20	009	Checklist -2022-0	
4 5 Section/topic	#	Checklist item	Reported on page #
7 TITLE		191	
⁸ 9 Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
		Ξ Φ Φ	
11 12 Structured summary 13 14	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
17 Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
18 Objectives 19	4	Provide an explicit statement of questions being addressed with reference to participants, in Firventions, comparisons, outcomes, and study design (PICOS).	5
20 METHODS		tp://	
22 Protocol and registration23	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
24 25 26	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
27 Information sources 28	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
29 30 31	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
32 Study selection 33	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
³⁴ Data collection process 35 36	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
37 Data items 38	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and $\frac{H}{2}$ and $\frac{H}{2}$ assumptions and simplifications made.	6
 ³⁹ Risk of bias in individual ⁴⁰ 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
42 Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
43 Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including net asures of consistency (e.g., I ²) for each meta-analysis.	7



PRISMA 2009 Checklist

Page	1	of 2	2
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		Page 1 of 2	
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		20.	
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		9 9	
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. 42 doi:10.1371/journal.pmed1000097 43 For more information, visit: www.prisma-statement.org. 44

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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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2 3 4	1	Adverse effects of non-steroidal anti-inflammatory drugs in
5 6 7	2	patients with viral respiratory infections: Rapid systematic review
8 9 10	3	Peter von Philipsborn, ^{1,2} Renke Biallas, ^{1,2} Jacob Burns, ^{1,2} Simon Drees, ³ Karin Geffert, ^{1,2} Ani Movsisyan, ^{1,2}
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60		1

15 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.

19 Design: Rapid systematic review

20 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.

Solution
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2 3	40	Registration: Registered with PROSPERO (CRD42020176056) and the Open Science Framework
5 4 5	41	(osf.io/snrp4).
6 7	42	
8 9 10	43	Keywords: non-steroidal anti-inflammatory drugs, viral respiratory infections, adverse effects, side
10 11 12	44	effects, COVID-19
13 14	45	
15 16 17	46	Article Summary
18 19	47	Character and limitations of this study.
20	47	Strengths and limitations of this study:
21 22 23	48	• We conducted a rapid systematic review following Cochrane rapid review guidance and the
24	49	PRISMA guideline
25 26 27	50	We systematically searched three databases and conducted forward- and backward-citation
28 29	51	searches
30 31 22	52	• We followed a pre-specified protocol, and clearly state where we deviated from it
32 33 34	53	• This is a rapid review, and we applied less quality controls than in the reviews we normally
35 36 37 38 39 40 41	54	conduct
	55	 The review is limited to studies in patients with viral respiratory infections and conditions
	56	commonly caused by respiratory viruses; we excluded studies on adverse effects of NSAIDs in
41 42 43	57	patients with bacterial respiratory infections, which have been summarised in existing reviews
44	58	
45 46 47	59	Wordcount: 3,454 words
48 49	60	
50 51 52	61	Background
53 54 55	62	
56 57	63	Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs, and have a
58 59 60	64	wide range of uses, including treatment of acute and chronic pain, fever, and inflammation. NSAIDs include
		3

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 bleeding¹ and renal damage,⁴ as well as elevated cardiovascular risks for some NSAIDs.¹⁵ 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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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

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130 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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1 2 2	142	as these studies best addressed the commissioned review question. For the remaining studies in children,
3 4 5	143	we mapped the evidence, i.e. we extracted and tabulated data on key study characteristics and adverse
6 7	144	outcomes, but did not assess risk of bias and certainty of evidence.
8 9	145	
10 11 12	146	We had originally planned to extract data on two sets of secondary outcomes (laboratory measures and
13 14	147	imaging findings), but decided that this was not feasible within the timeframe of the review. We had
15 16	148	intended to undertake meta-analyses and present forest plots of sufficiently similar studies. This was not
17 18 19	149	feasible in view of substantial heterogeneity in the interventions and outcomes assessed. We therefore
20 21	150	summarised findings narratively and through tables.
22 23	151	
24 25	152	We extracted and report all measures of treatment effect for the primary outcomes pre-specified in our
26 27 28	153	protocol. For dichotomous outcomes this includes risk ratios (RRs) and odds ratios (ORs). We extracted
20 29 30	154	and report adjusted results as provided by the included studies. We included 95% confidence intervals
31 32	155	(Cls) when these were reported by primary studies.
33 34 25	156	
35 36 37	157	Availability of data and materials
38 39 40	158	The data supporting the conclusions of this article are included within the article and its additional file.
41 42	159	Role of the funding source
43 44	160	Role of the funding source
45 46	161	
47 48 49	162	This review was funded through staff positions and university funds at the Ludwig-Maximilians- Universität
50 51	163	Munich, Germany. The review question was set by WHO, who requested this review from the Chair of
52 53	164	Public Health and Health Services Research at the LMU Munich in its capacity as a WHO Collaborating
54 55 56	165	Centre for Evidence-Based Public Health. The authors alone are responsible for the views expressed in this
50 57 58	166	article and they do not necessarily represent the decisions, policy or views of the WHO.
59 60	167	

¢

1 2	168	Patient and public involvement
3	100	
4 5 6	169	Patients and the public were not involved in this study.
7 8	170	
9 10 11	171	Results
12 13 14	172	
14 15 16	173	Results of the search
17 18	174	
19 20	175	The PRISMA flow chart is shown in Figure 1, and the search log is shown in the supplementary appendix.
21 22 23	176	Through database and forward- and backward-citation searches we identified 10,999 unique records. Of
24 25	177	these, we excluded 10,196 at title and abstract screening stage, leaving 803 studies to be assessed as full
26 27	178	texts. We were able to locate and assess the full texts for 738 studies. Overall, 87 studies met the eligibility
28 29	179	criteria and were included in our review.
30 31 32	180	
33 34	181	We included 72 RCTs, seven cohort studies, three case-crossover studies, three non-randomised
35 36	182	controlled trials (NRCTs), one case-control study and one case series. The total number of participants was
37 38	183	172,381 (median: 174, range: 20 to 83,915). The median follow-up was 3 days (range: 1 hour to 11
39 40 41	184	months). We did not identify any study on COVID-19, SARS or MERS meeting the eligibility criteria. All
42 43	185	studies related to other acute viral infections, or to conditions, such as upper respiratory tract infections,
44 45	186	that are commonly caused by respiratory viruses.
46 47	187	
48 49 50	188	We included 39 studies in our evidence synthesis, and 48 studies in our evidence mapping. Studies
50 51 52	189	included in the evidence synthesis comprised 28 RCTs, three cohort studies ²⁶⁻²⁸ and two case-crossover
53 54	190	studies ⁸⁹ in adults, and three case-control studies ^{29 30} and four studies reporting on one RCT in children. ³¹⁻
55 56	191	³⁴ One retrospective cohort study ²⁷ and one RCT ²¹ included both adults and children. The latter included
57 58	192	participants aged three years and older, and did not report results separately for adults and children. With
59 60	193	the majority being adults, we included this study in the evidence synthesis for adults. We assessed most 8

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194	of the studies to be at high or unclear risk of bias in at least one domain. Risk of bias of case-control and
195	case-crossover studies is shown in Figure 2, and risk of bias of all other study designs in Figure 3. Studies
196	included in evidence mapping comprised 39 RCTs, four cohort studies, four NRCTs and one case series in
197	children. Details on the population, intervention and comparison, outcomes and study designs of included
198	studies are provided in the supplementary appendix.
199	
200	Findings for adults
201	
202	Summary of findings for the effects of NSAIDs on mortality and cardiovascular events in adults with viral
203	respiratory infections are shown in Table 3. Effects on the rate of re-consultations with general
204	practitioners are shown in Table 4.
205	
206	One retrospective registry-based cohort study in 683 adults with a follow-up of 60 days reports effects on
207	mortality. ²⁷ Results indicate that the effects of NSAIDs on mortality in critically ill adults with influenza
208	during the 2009/2010 H1N1 influenza pandemic are unclear (adjusted risk ratio (aRR): 0.9, 95% CI: 0.5-
209	1.6). The confidence interval for this effect estimate is large and includes the possibility of a negative, null
210	or positive effect. This evidence was graded as very low certainty. The same conclusion (very low certainty
211	evidence) is suggested for a subgroup analysis for aspirin only (data shown in Table s1 in the
212	supplementary appendix).
213	
214	Two case-crossover studies in 9,793 patients with myocardial infarction and 29,518 patients with ischemic
215	or hemorrhagic stroke assessed effects on cardiovascular events. ⁸⁹ Both studies report multiple indirect
216	comparisons, comparing adults without acute respiratory infection and not exposed to NSAIDs to: i) adults
217	exposed to both an acute respiratory infections and NSAIDs; ii) adults with an acute respiratory infection
218	but not exposed to NSAIDs; and iii) adults without an acute respiratory infection but exposed to NSAIDs.
219	Both studies report higher odds ratios (ORs) for the combined exposure to NSAIDs and acute respiratory
	 195 196 197 198 199 200 201 202 203 204 205 206 207 208 209 210 211 212 213 214 215 216 217 218

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 RCTs²¹²²³⁵⁻⁶⁰ and two cohort studies²⁶²⁸ 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.^{2235373941424447.4952.5659} 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 syncopation⁴³ 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)

2 3	246	(OR 1.7, 95% CI: 1.1 to 2.4). The study reports that "[m]ost of the 17 'complications' recorded were not
5 4 5 6 7	247	serious". ²¹ This evidence was considered to be of low certainty due to study limitations and indirectness
	248	of evidence.
8 9	249	
10 11 12	250	Findings for children
13 14	251	
15 16	252	Summary of findings for effects of NSAIDs on mortality and risk for empyema, gastrointestinal bleeding,
17 18 19	253	death from all causes and hospitalisation in children are shown in Tables s2 and s3 in the supplementary
19 20 21	254	appendix.
22 23	255	
24 25 26 27 28 29 30	256	One cohort study in 838 children (mean age: 7 years) with a follow-up of 60 days reports effects on
	257	mortality. ²⁷ Results indicate that the effects of NSAIDs on mortality in critically ill children with H1N1
	258	influenza are unclear (aRR 1.5, 95% CI: 0.7-3.2; very low certainty evidence).
31 32	259	
33 34	260	One matched case-control study in 166 children aged 3-15 years with acute viral infections reports effects
 35 36 37 38 39 40 41 42 43 44 45 46 	261	on risk for empyema (follow-up: 15 days). ³⁰ One case-crossover study in 177 children (aged 2 months to
	262	16 years) with fever reports effects on gastrointestinal bleeding (follow-up: 7 days). ²⁹ Results indicate that
	263	children with empyema and gastrointestinal bleeding may be more likely to have been exposed to NSAIDs
	264	than children without these conditions (aOR for empyema: 2.8, 95% CI: 1.4-5.6; aOR for gastrointestinal
	265	bleeding: 8.2, 95% CI: 2.6-26.0; very low certainty evidence). ^{29 30}
40 47 48	266	
49 50	267	Four studies on one RCT including 83,915 children report effects on death from all causes and risk for
51 52	268	hospitalisation (follow-up: 4 weeks), comparing ibuprofen with acetaminophen (paracetamol). ³¹⁻³⁴ The
53 54 55	269	study had 80% power to detect a 0.2 percentage point difference in hospitalisation for any cause, and
55 56 57	270	differences of 1 per 10,000 for hospitalisation for acute gastrointestinal bleeding, acute renal failure and
58 59	271	anaphylaxis. Our assessment of the certainty of evidence for differences between the ibuprofen and the
60		

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.

P.J.C.

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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2 3	298	
5 4 5 6 7	299	We identified 56 eligible studies in children. Most of these were small and of short duration, and provide
	300	only limited evidence on severe adverse effects. One large RCT in children provides moderate to high
8 9 10	301	certainty evidence that the difference in the rate of death from all causes and of hospitalisation for acute
10 11 12 13 14	302	renal failure and anaphylaxis is likely to be smaller than 1 per 10,000, that the difference in hospitalisation
	303	for acute gastrointestinal bleeding is likely to be smaller than 2 per 10,000, and the difference in
15 16	304	hospitalisation for any cause less than 20 per 10,000. ³¹⁻³⁴
17 18 19	305	
20 21	306	We did not identify any studies reporting on measures of inpatient healthcare utilisation, long-term
22 23	307	survival or explicit quality of life measures.
24 25 26 27 28 29 30	308	
	309	This is a rapid review, conducted over two weeks, with a number of limitations:
	310	• Searches were limited to three databases, i.e. MEDLINE, EMBASE and the WHO COVID-19
31 32	311	database, complemented with forward- and backward-citation searches. We did not search for or
 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 	312	include sources of grey literature or pre-prints, and considered only studies published in English
	313	or German.
	314	• Screening criteria and guidance were refined and calibrated while screening was underway, and
	315	only 20% of titles and abstracts and 50% of full texts were screened in duplicate.
	316	• Data extraction and risk of bias assessment were done by one review author only. To account for
	317	potential errors, all data presented in tables or figures as part of the evidence synthesis were
	318	checked for their correctness by a second review author.
49 50	319	• Risk of bias assessment and full evidence synthesis was limited to studies in adults and to those
51 52	320	studies in children most capable of detecting rare severe adverse events (i.e. case control studies
53 54	321	and large RCTs). The decision to exclude other studies in children from evidence synthesis was
55 56 57 58 59 60	322	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 reviews⁶³ and were beyond the scope of this rapid review. NSAIDs constitute a diverse group of drugs with diverging risk profiles for different populations and conditions. Not all studies distinguished between different types of NSAIDs. Some of the older studies are likely to have included patients taking NSAIDs that are no longer available on the market due to their known side effects. Some studies provided only indirect comparisons, which can be informative, but do not provide effect estimates for the actual comparison of interest, i.e. NSAID use vs. no NSAID use among individuals with a viral respiratory infection.89 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

1 2 2	348	underpowered for detecting rare severe adverse events, and from case-control and cohort studies
3 4 5	349	with methodological limitations.
6 7	350	
8 9 10	351	Conclusions
11 12 13	352	We did not find conclusive evidence showing that NSAIDs in patients with viral respiratory infections are
14 15	353	associated with additional risks for severe acute adverse outcomes, above and beyond the known risks
16 17	354	associated with NSAIDs alone and viral respiratory infections alone. This absence of evidence should not
18 19	355	be interpreted as evidence for the absence of such risks. Most of the evidence was of very low to low
20 21 22	356	certainty, and should be interpreted with caution. To improve the evidence base, future studies should
23 24	357	use robust study design, sufficiently large sample sizes and follow-up periods, and follow relevant
25 26	358	reporting guidelines. When using NSAIDs, existing guidance should be considered, including approved
27 28	359	product information for specific NSAIDs and relevant clinical guidelines.
29 30 31	360	
32 33	361	Captions:
34 35	362	Figure 1: PRISMA flow chart
36 37	363	Figure 2: Risk of bias of case-control and case-crossover studies
38 39 40	364	• Figure 3: Risk of bias of studies other than case-control and case-crossover studies
40 41 42	365	Table 1: Inclusion criteria
43 44	366	Table 2: Exclusion criteria
45 46	367	• Table 3: Summary of findings for the effects of NSAIDs on mortality and cardiovascular events in
47 48 49	368	adults with viral respiratory infections
50 51	369	• Table 4: Summary of findings for the effects of NSAIDs on the rate of re-consultations with
52 53	370	general practitioners in patients with acute respiratory infections
54 55	371	
56 57 58	372	Tables
58 59 60	373	
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374 Table 1

4 375

Population	Humans of any age with acute	Patients with COVID-19 / SARS-CoV-2
	viral respiratory infections, with	Patients with SARS / MERS
	or without co-morbidities (e.g.	Patients with other coronavirus infections
	cardiovascular disease, diabetes	Patients with other acute viral respiratory infections,
	mellitus, COPD, asthma)	including influenza, parainfluenza and rhinovirus infe
		Patients with conditions commonly caused by respira
		viruses, including children with fever and patients of a
		age with upper respiratory tract infections, including
		common cold, pharyngitis, laryngitis, sore throat and
		tonsillitis, unless specified as being of bacterial etiolog
		treated with antibiotics
Intervention	Non-steroidal anti-	Unselective COX inhibitors: ibuprofen, aspirin
/ Exposure	inflammatory drug (NSAID)	(acetylsalicylate), diclofenac, naproxen, indomethacin
	intake prior or during the acute	ketoprofen, etc.
	infection, including oral,	
	intravenous and intramuscular	
	NSAIDs and NSAIDs as	Selective COX 2 inhibitors: Celecoxib, Rofecoxib, Etori
	suppositories taken or	Lumiracoxib, and Valecoxib, etc.
	administered for any reason (including treatment of	
	underlying conditions, and	
	treatment of fever, pain and	4
	other acute symptoms)	
Comparison	No or different NSAID	No NSAID (including other antipyretic and analgesic d
companison		e.g. paracetamol/ acetaminophen)
		Different dose or application of NSAID
		Different NSAID (e.g. aspirin versus ibuprofen)
Outcomes	Acute severe adverse events,	Acute severe adverse events:
	acute healthcare utilization and	Mortality
	longer-term effects	• Acute respiratory distress syndrome (ARDS)
		Acute organ failure (including acute renal failure)
		Cardiovascular events
		Opportunistic infections
		Severe acute allergic and hypersensitivity reactio
		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	Randomized controlled trials
Study designs	Any systematic empirical study design	Randomized controlled trials Cohort studies Case-control-studies

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 including gastrointestinal effects and renal damage associated with long-term u any NSAID, and cardiovascular risks due to selective cyclooxygenase (COX) 2 inhand diclofenac, as these are well established Allergic and hypersensitivity reactions occurring in general, i.e. in the absence or respiratory infections 		Case series with < 10 patients (only for COVID-19, SARS and MERS)
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 / 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 infect including gastrointestinal effects and renal damage associated with long-term u any NSAID, and cardiovascular risks due to selective cyclooxygenase (COX) 2 infrand diclofenac, as these are well established Allergic and hypersensitivity reactions occurring in general, i.e. in the absence or respiratory infections Reye's syndrome and Kawasaki syndrome, as these represent well-studied condoutside the scope of this review Implicit quality of life measures (e.g. pain, nasal congestion) 	Table 2	
 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 / 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 infect including gastrointestinal effects and renal damage associated with long-term u any NSAID, and cardiovascular risks due to selective cyclooxygenase (COX) 2 infrand diclofenac, as these are well established Allergic and hypersensitivity reactions occurring in general, i.e. in the absence or respiratory infections Reye's syndrome and Kawasaki syndrome, as these represent well-studied contoutside 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 	Table 2: Exclusior	n criteria
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 infect including gastrointestinal effects and renal damage associated with long-term u any NSAID, and cardiovascular risks due to selective cyclooxygenase (COX) 2 infr and diclofenac, as these are well established ••Allergic and hypersensitivity reactions occurring in general, i.e. in the absence or respiratory infections ••Reye's syndrome and Kawasaki syndrome, as these represent well-studied cond outside the scope of this review ••Implicit quality of life measures (e.g. pain, nasal congestion)Study designs••Mechanistic data	Population	 Patients with non-respiratory viral infections Patients with hemorrhagic fevers (including Dengue and Ebola) Patients with infections treated with antibiotics
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Study designs • Non-empirical studies (e.g. commentaries) • Animal studies • Mechanistic data	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 inhibit and diclofenac, as these are well established Allergic and hypersensitivity reactions occurring in general, i.e. in the absence of vir respiratory infections Reye's syndrome and Kawasaki syndrome, as these represent well-studied conditio outside the scope of this review
	Study designs	 Non-empirical studies (e.g. commentaries) Animal studies Mechanistic data

383 Table 3

Patient or population: adult Intervention: use of NSAIDs Comparison: no use of NSAI	s with acute respiratory infections (ARI) Ds	_	
Outcomes	Impact	№ of participants (studies)	Certainty the evide (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 LO
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 LO
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 LO
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 LO

2 38 3 20

1 2 3 4 5 5 6 7 7 8 9 9	GRADE Working Group grades of evidence High certainty: We are very confident that the Moderate certainty: We are moderately com estimate of the effect, but there is a possibilit Low certainty: Our confidence in the effect of the estimate of the effect Very low certainty: We have very little confit substantially different from the estimate of the	fident in the effect estimate: The true ef ity that it is substantially different estimate is limited: The true effect may b dence in the effect estimate: The true eff	fect is likely to e substantially	be close to t different fro
1 385 2 386 3 4 387 5	Explanations: a. Downgraded by 1 level for Table 4	or imprecision.		
16 388 17 18 19	Table 4: Use of ibuprofen vs. paracetam infections	nol in participants aged ≥3 years with	acute respira	atory tract
20 21 22 23 24	Patient or population: participants aged ≥3 Intervention: use of ibuprofen Comparison: use of paracetamol	years with acute respiratory tract infection	ons	
24 25 26 27 28 29	Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
30 31 32 33	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)	
34 35 36 37 38 39 40 41 42 43	GRADE Working Group grades of evidence High certainty: We are very confident that the Moderate certainty: We are moderately con- the estimate of the effect, but there is a poss Low certainty: Our confidence in the effect efform the estimate of the effect Very low certainty: We have very little confi substantially different from the estimate of effort	fident in the effect estimate: The true ef sibility that it is substantially different estimate is limited: The true effect may b dence in the effect estimate: The true eff	fect is likely to e substantially	be close to different
14 389 15 390 16 391 17 392 18 393 10 394 12 394 15 394 15 366 16 394 17 394 18 394 19 394 10 394 10 394 11 394 12 394 13 394 14 355 15 366 15 366 16 37 16 38	Explanations a. Downgraded evidence by 1 level for stu b. Downgraded evidence by 1 level for inc		2.	
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7 8 9	397	Not applicable
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¹³ 426 Licence statement

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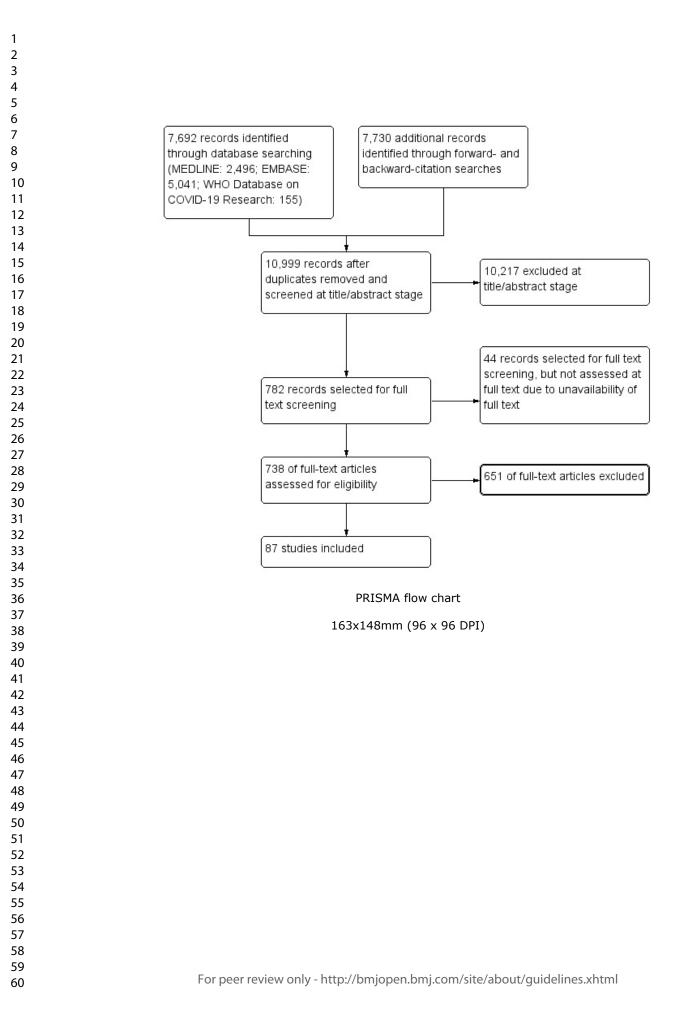
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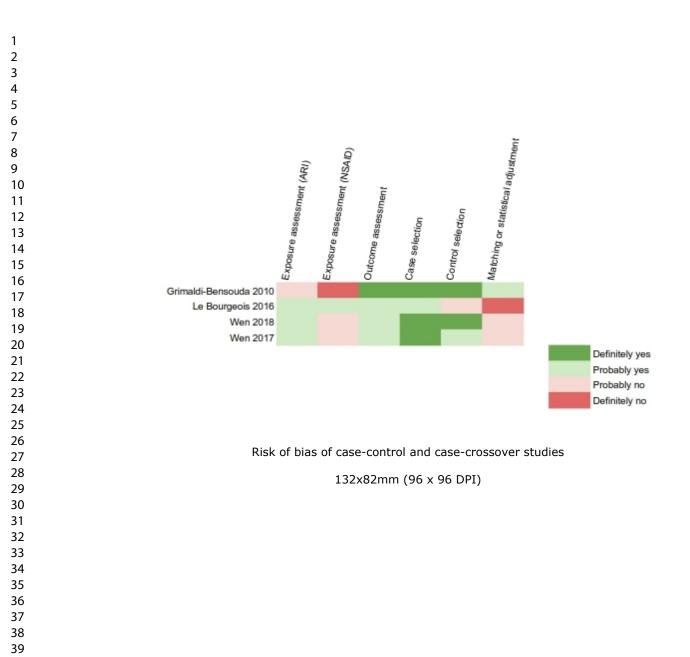
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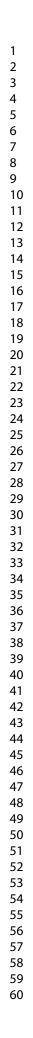
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Risk of bias of studies other than case-control and case-crossover studies

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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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	 Search strategy for EMBASE Search strategy for the WHO COVID-19 Research Database References used for forward- and backward-citation searches Data extraction form Search log Potentially relevant studies for which no full text could be obtained References of included studies Characteristics of studies included in the evidence synthesis Effects on primary outcomes reported by studies included in the evidence synthesis Characteristics of and outcomes reported in studies included in the evidence mapping Sub-group analyses (table s1)

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/	1136
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.	2430
38	exp Severe Acute Respiratory Syndrome/	4460
39	or/35-38	2594
40	exp Influenza, Human/	4826
41	exp Influenzavirus A/	4317
42	exp Influenzavirus B/	4211
43	(influenza* not h?em?phil* influenza*).ti,ab,kf.	9570
44	(flu or H1N1 orH2N2 or H3N2 or H1N12 or H5N1).ti,ab,kf.	2452
45	or/40-44	1110
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/	3523
51	viral respiratory tract infection*.mp.	385
52	urti.ti,ab,kf.	855
53	viral respiratory infection.mp.	261
54	(respiratory adj2 virus).mp.	1893
55	(respiratory adj2 viral).mp.	4736
56	Rhinitis/	1247
57	rhinitis.ti,ab,kf.	2738
58	exp Pharyngitis/	1552
59	pharyngitis.ti,ab,kf.	5754
60	RSV.mp.	1171
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.	1411
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	4042
74	(respiratory distress syndrome or ARDS or lung injury).ti,ab,kf.	5045
75	exp Respiratory Distress Syndrome, Adult/	1898
76	or/74-75	5578

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

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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).mp.	12135
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/	20722
9	aspirin.mp.	11611
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

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.	92627
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
	rhinitis/	18800
73		
73 74	pharyngitis/	15196

rhinopharyngitis/	12432
laryngitis/	3672
laryngit*.ti,ab.	1987
nasopharyngit*.ti,ab.	2472
or/66-79	109716
(virus or viral).mp.	1487387
80 and 81	13487
rhinovirus.ti,ab.	6844
exp rhinovirus/	8285
vir* pneumonia.ab,ti.	1760
exp virus pneumonia/	14441
exp viral respiratory tract infection/	3869
exp parainfluenza virus infection/	1261
exp Human respiratory syncytial virus/	4427
respiratory syncytial virus.mp.	19005
or/83-90	42933
55 or 60 or 65 or 82 or 91	213662
43 and 92	6543
animal/ not human/	1061398
93 not 94	6525
(english or german).lg.	2990274
95 and 96	6214
limit 97 to (article or article in press or erratum or letter or note or "review" or short survey)	5041
	laryngit*.ti,ab. nasopharyngit*.ti,ab. or/66-79 (virus or viral).mp. 80 and 81 rhinovirus.ti,ab. exp rhinovirus/ vir* pneumonia.ab,ti. exp virus pneumonia/ exp virus pneumonia/ exp viral respiratory tract infection/ exp parainfluenza virus infection/ exp Human respiratory syncytial virus/ respiratory syncytial virus.mp. or/83-90 55 or 60 or 65 or 82 or 91 43 and 92 animal/ not human/ 93 not 94 (english or german).lg. 95 and 96 limit 97 to (article or article in press or erratum or letter or note or "review" or short survey)

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 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 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

 Buchanan W, Bellamy N: NSAIDs: Clinical efficacy and toxicity. InflammoPharmacology 1991, 1(2):115-133.

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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

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

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 s	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	n 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	65
text	
text Excluded at full text screening stage	654

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9. Characteristics of studies included in the evidence synthesis

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9. Charad	cteristics o	f studies included in the evider	nce synthesis					
Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Noven design	Follow-up	Outcome
Azuma 2010	Japan	<u>N</u> : 170 adults <u>Age range</u> : 20-70 years <u>Mean age</u> : n.r. <u>Disease</u> : Upper respiratory tract infection (URTI)	Zaltoprofen, Placebo	Pain and fever relief	<u>Dosage</u> : Zaltoprofren 1: 160mg Zaltoprofren 2: 80mg <u>Application</u> : oral <u>Frequency</u> : once	ber 2020. Downlo	6 hours	Counts of Adverse Effects (AEs): Symptoms after administration of study medication
Azuma 2011	Japan	<u>N</u> : 330 adults <u>Mean age</u> : Zaltoprofen: 33 years Loxoprofen: 36 Placebo: 36 <u>Age range</u> : 20-70 years <u>Disease</u> : Febrile URTI	Zaltoprofen, Loxoprofen, Placebo	Pain and fever relief	Dosage: Zaltoprofen: 160 mg Loxoprofen: 60mg <u>Application</u> : oral <u>Frequency</u> : once	RCT RCT Aded from http://bmjope	4 hours	Counts of AEs: Symptoms after administration of study medication
Bachert 2005	Russia	<u>N</u> : 392 adults <u>Age range</u> : 18 - 65 years <u>Mean age</u> : 37.4 years <u>Disease</u> : Febrile URTI	Aspirin, Acetaminophen, Placebo	Pain and fever relief	Dosage: Aspirin 1: 500mg Aspirin 2: 1000mg Acetaminophen 1: 500mg Acetaminophen 2: 1000mg <u>Application</u> : oral <u>Frequency</u> : once	.bmj.com/ on April 17, 2	6 hours	Counts of (severe) AEs
Bettini 1986	Italy	<u>N</u> : 120 adults <u>Age range</u> : n.r. <u>Mean age:</u> 37 years <u>Disease: I</u> nfluenza-related fever	Diclofenac, Aspirin	Fever relief	Dosage: 1) Diclofenac 25 mg 2) Aspirin 500 mg <u>Application</u> : oral <u>Frequency</u> : 1) every 12 hours for two days 2) every 8 hours for two days	RCT 2024 by guest. Protect	2 days	Count of AEs: Medication side effects
Boureau	France	<u>N</u> : 113 adults	lbuprofen,	Symptom	Dosage: Ibuprofen: 400mg		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		<u>Age range</u> : 18-60 years <u>Mean age</u> : n.r. <u>Disease</u> : Tonsillitis	Paracetamol	relief	Paracetamol: 1000mg Application: oral Frequency: once	-		symptoms after administration o study medication
Broggini 1986	Italy	<u>N</u> : 30 adults <u>Age range</u> : n.r. <u>Mean age</u> : Flurbiprofen 34.4 years; Aspirin 41.6 years <u>Disease:</u> Influenza	Flurbiprofen, aspirin	Symptom relief	Dosage: Application: oral 1) Flurbiprofen Frequency: twice daily over four days		4 days	Count of AEs: Medication side effects
Ebel 1985	USA	<u>N</u> : 312 adults <u>Age range</u> : 18 - 70 years <u>Mean age</u> : male: 38.5 years female 43.5 <u>Disease</u> : URTI	Sulindac, Placebo	Symptom relief	Dosage: Sulindac 200mg Application: n.r. Frequency: twice per day, 7 days		7 days	Counts of (sever AEs
Eccles 2003	Sweden, UK	<u>N</u> : 279 adults <u>Age range</u> : 18-60 years <u>Mean age</u> : IG 25.5 years CG 24.5 years <u>Disease</u> : 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	<u>N</u> : 833 participants <u>Age range</u> : n.r. <u>Mean age</u> : n.r. <u>Disease</u> : URTI	Aspirin + Pseudoephedrine, Aspirin, Pseudoephedrine, Placebo	Symptom relief	Dosage:1) 500 mg ASA + 30 mgPSE2) 500 mg ASA2) 500 mg ASA443) 60 mg PSE50Application:oralFrequency:2-3 doses on day 1, 3doses for another 3 days50		7 days	Counts of AEs
Epperly 2016	USA	<u>N</u> : 683 adults 838 children;	NSAIDs, Aspirin,	Improvemen t of the	<u>Dosage</u> : n.r. <u>Application</u> : most likely oral intake	Retrospe	Adults: 60 days	Risk of mortality

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Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	040990 on 1	Study design	Follow-up	Outcome
		Age range: n.r. <u>Mean age:</u> 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 <u>Disease</u> : pH1N1	non-use	medical course of influenza	<u>Frequency</u> : n.r.	B November 2020. Downloaded	stry- based cohort study	Children: 90 days	
Gehanno 2003	France	<u>N</u> : 343 <u>Age range</u> : 20-60 years <u>Mean age</u> : 40 years <u>Disease</u> : Febrile sore throat	Diclofenac potassium, Paracetamol	Pain and fever relief	<u>Dosage</u> : Diclofenac potassium 6.25 mg, 12.5 mg and 25 mg Paracetamol: 1000 mg <u>Application</u> : Oral <u>Frequency</u> : Once	d from http://bmjo	RCT	10 days	Counts of AEs
Goto 2007	Japan	<u>N</u> : 189 <u>Age group</u> : 18-65 years <u>Mean age</u> : Loxoprofen: 29.3 years, Placebo 27.6 years <u>Disease</u> : 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	pen.bmj.com/ on Apri	RCT	7 days	Counts of AEs
Graham 1990	Australia	<u>N</u> : 60 adults <u>Age range</u> : 18 - 30 years <u>Mean age</u> : n.r. <u>Disease</u> : URTI	Aspirin, Acetaminophen, Ibuprofen	Symptom relief	Dosage: Aspirin: 500mg Acetaminophen: 500mg Ibuprofen: 200mg <u>Application</u> : Oral <u>Frequency</u> : Daily for 7 days Aspirin: 4 doses Acetaminophen: 4 doses Ibuprofen: 3 doses	17, 2024 by guest. Protected by	RCT	28 days	Counts of AEs: Symptoms after administration of study medication
Grebe	Germany	<u>N</u> : 356 adults	Diclofenac-K,	Symptom	Dosage: Diclofenac-K: 12.5mg,	ted by	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 <u>Application</u> : oral <u>Frequency</u> : 3 days	-		
Grimaldi- Bensouda 2010	France	<u>N</u> : 177 children <u>Age range</u> : 2 months - 16 years <u>Mean age</u> : n.r. <u>Disease</u> : 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	cross- over study	7 days	Risk of upper gastrointestinal bleeding
Grunthal 2008	Germany	<u>N</u> : 2341 <u>Age range</u> : n.r. <u>Mean age</u> : ca. 40 years <u>Disease</u> : 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 maleat3) chlorphenamin maleat(2,5 mg)+ vitamin C(150 mg)Application:oralFrequency:1) mean:1.6 doses2) mean:2) mean:1.9 doses		3 days	Counts of AEs
Hung 2017	Hong Kong	<u>N</u> : 217 adults <u>Age range:</u> ≥ 18 years <u>Median</u> : 80 years <u>Disease</u> : Influenza A (H3N3)	Clarithromycin + Naproxen + Oseltamivir, Oseltamivir	Treatment of severe influenza	Dosage: 1) triple combination Get (Clarithromycin 500 mg + Homoson 200 mg + Oseltamivir 75 mg) Homoson 200 mg + Oseltamivir 2) Oseltamivir 75 mg Homoson 200 mg + Oseltamivir Application: oral Get		30 days	Risk for Mortalit (at 30 / 90 days) duration of hospitalization
								29

				BMJ Open	<u>`</u>	miopen-2020-040990 Study		Page
Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	040 990 Study design	Follow-up	Outcome
					Group 2: 2) twice daily for five days	9 November 2020. Do		
Le Bourgeois 2016	USA	<u>N</u> : 166 children <u>Age range</u> : 3 -15 years <u>Mean age</u> : Cases: 4.1 ± 2.3 Controls: 3.8 ± 2.3 <u>Disease</u> : Acute viral infection (upper respiratory tract viral infections, lower respiratory tract viral infections and others)	Ibuprofen, Ketoprofen, non-use	Relief of symptoms	<u>Dosage</u> : n.r. <u>Application</u> : n.r. <u>Frequency</u> : 1, 2 and 3 consecutive days intake of Ibuprofen or Ketoprofen	Matched case- control study	Cases and controls: 15 days (retrospectiv e)	Risk of hospitalization (empyema)
Lesko 1995	USA	<u>N</u> : 83,915 children <u>Age range</u> : 6 months - 12 years <u>Mean age</u> : n.r. <u>Disease</u> : Febrile illness	Ibuprofen, Paracetamol	Relief of symptoms of febrile illness	Ibuprofen 2: 10mg/kg Paracetamol: 10 mg/kg <u>Application</u> : oral <u>Frequency</u> : Ibuprofen 1 and 2: median number of doses 6-10, median	Randomi zed Controlle d Trial (RCT) 7. 2024 by quest. Protected by RCT	4 weeks	Risk of hospitalization for acute gastrointestinal bleeding, acute renal failure, anaphyla xis or Reye's syndrome Counts of other (severe) AEs leading to hospitalization
Lesko	USA	<u>N</u> : 288 children	Ibuprofen,	Relief of	Dosage: Ibuprofen 1: 5mg/kg	RCT	4 weeks	Risk of renal
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99				BMJ Open	Medication details			
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 <u>Application</u> : oral <u>Frequency</u> : All: median number of doses 7, median duration 2 days			impairment
Lesko 1999	USA	<u>N</u> : 27,065 children <u>Age range</u> : 1 - 23 months <u>Mean age</u> : n.r. <u>Disease</u> : Febrile illness	Ibuprofen, Acetaminophen	Relief of symptoms of febrile illness	Dosage: Ibuprofen 1: 5mg/kg Ibuprofen 2: 10mg/kg Acetaminophen: 12mg/kg <u>Application</u> : oral <u>Frequency</u> : All: median number of doses 6-100 median duration 3 days		4 weeks	Risk of hospitalization f acute gastrointestinal bleeding, acute renal failure, anaphyl xis or Reye's syndrome Counts of other (severe) AEs leading to hospitalization
Lesko 2002	USA	<u>N</u> : 1879 children <u>Age range</u> : 6 months - 12 years <u>Mean age</u> : n.r. <u>Disease</u> : Febrile illness	lbuprofen, Acetaminophen	Relief of symptoms of febrile illness	Dosage: Ibuprofen 1: 5mg/kg Ibuprofen 2: 10mg/kg Acetaminophen: 12mg/kg <u>Application</u> : Oral <u>Frequency</u> : n.r.	RCT	4 weeks	Risk of outpatien visits or hospitalization f asthma
Little 2013	UK	<u>N</u> : 89 children and adults <u>Age range</u> : ≥ 3 years <u>Mean age</u> : Ibuprofen 34; Paracetamol 34; Both 33	Ibuprofen, Paracetamol, Ibuprofen + Paracetamol	Symptom relief	Dosage: n.r. Application: Oral Application: Oral Topologication: Oral Frequency: Dependent on trial Topologication: Oral arm; Regular dosing: 4x daily; As Topologication: Oral required dosing: as required by Topologication: Oral	RCT	28 days	Healthcare utilization: retur visit with new of worsening symptoms or
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				BMJ Open		mjopen-2020-040990			Page 6
Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details)-040990 on 7	Study design	Follow-up	Outcome
		<u>Disease</u> : Respiratory infections (upper and lower)			symptoms up to 4x daily	19 Novem			complicationsof intervention
Llor 2013	Spain	<u>N</u> : 416 <u>Age range</u> : 18-70 years <u>Mean age</u> : 45.1 years <u>Disease</u> : RTI	Ibuprofen, Amoxicillin- clavulanic acid, Placebo	Symptom relief	<u>Dosage</u> : Ibuprofen: 600 mg Amoxicillin-clavulanic acid: 500 mg <u>Application</u> : n.r. <u>Frequency</u> : 3 daily for 10 days	ber 2020. Downlo	RCT	11-13 days	Counts of AEs: events possible related to drug
Loose 2011	Germany	<u>N</u> : 640 adults <u>Age range</u> : not reported <u>Mean age</u> : 19.6 years <u>Disease</u> : URTI leading to nasal congestion	Aspirin + Pseudoephedrine, Paracetamol + Pseudoephedrine, Placebo	Symptom relief	<u>Dosage</u> :a) ASA + 60mg PSE b) ASA + 30mg PSE c) Paracetamol 1000 mg +60mg PSE d) Placebo <u>Application</u> : oral <u>Frequency</u> : once	aded fro	RCT	6 h	Counts of AEs
Milvio 1984	Switzerlan d	<u>N</u> : 50 adults <u>Age range</u> : n.r. <u>Mean age</u> : Nimesulide: 38 years; Benzydamine: 49 years <u>Disease</u> : Inflammation of the ear, nose and throat	Nimesulide, Benzydamine	Treatment of fever and inflammatio n	Dosage:1) Nimsulide 100 mg 2) Benzydamine 75 mg Application: oral <u>Frequency</u> : twice a day for 10 days	1.bmj.com/ on April 1.	RCT	10 days	Count of AEs: Medication side effects
Nouri 1993	Austria or Switzerlan d	<u>N</u> : 65 adults <u>Age range</u> : 35-62 years <u>Mean age</u> : IG: 39 years CG: 53 years <u>Disease</u> : Non-bacterial inflammation of the ear, nose and throat	Nimesulide, Naproxen	Treatment of inflammatio n	<u>Dosage</u> : 1) Nimseluide 100 mg 2) Naproxen 500 mg <u>Application</u> : oral <u>Frequency</u> : Twice daily, mean duration 8.7 days	, 2024 by guest. Protect	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	<u>N</u> : 940 children and adults <u>Age range</u> : 15-77 years <u>Mean age</u> : 38 years <u>Disease</u> : 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	<u>N</u> : 120 adults <u>Age range</u> : 18 - 88 years <u>Mean age:</u> Ibuprofen: 41.5 years, Acetaminophen: 46.1 <u>Disease</u> : Severe throat pain	Ibuprofen, Acetaminophen, Placebo	Symptom relief	Dosage: Ibuprofen: 400mg Overality Acetaminophen: 1000mg Dosage: Application: oral Overality Frequency: Once Overality		1 day	Counts of AEs
Schachtel 1991	USA	<u>N</u> : 210 adults <u>Age range</u> : 18 - 83 years <u>Mean age</u> : 30 <u>Disease</u> : Tonsillopharyngitis/URTI	Aspirin + caffeine, Aspirin, Placebo	Pain relief	Dosage: Aspirin 1: 800mg + 64mg Aspirin 2: 800mg Placebo Application: Oral Frequency: Once		2 hours	Counts of AEs
Schachtel 2007	USA	<u>N</u> : 197 adults <u>Age range</u> : ≥ 18 years <u>Mean age</u> : n.r. <u>Disease:</u> Tonsillopharyngitis	Valdecoxib, Placebo	Symptom relief	Dosage: No Valdecoxib 1: 40 mg Valdecoxib 2: 20 mg Valdecoxib 2: 20 mg Of Placebo Application: n.r. Frequency: once No	RCT	24 hours	Counts of AEs
Schachtel 2011	USA	<u>N</u> : 269 adults <u>Age range</u> : 18 - 30 <u>Mean age</u> : 19 <u>Disease</u> : 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	KC1	24 hours	Counts of AEs
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				BMJ Open		2020-040990 Study		Pag
Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	040990 Study design	Follow-up	Outcome
					6-12 hours <u>Application</u> : oral <u>Frequency</u> : once	9 November		
Smith 2014	USA	<u>N</u> : 207 adults <u>Age range</u> : 18 - 34 years <u>Mean age</u> : 21 years <u>Disease</u> : URTI	Ibuprofen + Caffeine, Ibuprofen, Caffeine, Placebo	Symptom relief	<u>Dosage</u> : Ibuprofen + Caffeine: 200mg + 100mg Ibuprofen: 200mg Caffeine: 100mg Placebo <u>Application</u> : Oral <u>Frequency</u> : once	RCT 2020. Downloaded from	3 hours	Counts of AEs
Sperber 1989	USA	<u>N</u> : 58 adults <u>Age range</u> : n.r. <u>Mean age</u> : 20-21 years <u>Disease</u> : Cold	Ibuprofen + Pseudoephedrine, Pseudoephedrine Placebo	Symptom relief	Dosage: Pseudoephidrine + Ibuprofen: 60mg + 200mg Pseudoephidrine 60mg Placebo <u>Application</u> : Oral <u>Frequency</u> : 2 doses the first day, 4 doses over next 4 days	http://bmiopen.bmi.com/	14 days	Counts of AEs: symptoms after administration o study medicatior
Sperber 1992	USA	<u>N</u> : 87 adults <u>Age range</u> : n.r <u>Mean age</u> : 21.4 years <u>Disease</u> : Cold	Naproxen, Placebo	Symptom relief	Naproxen 1: 1 loading dose (400mg) + 3 times daily 200mg fo 5 days Naproxen 2 and 3: 1 loading dose (500mg) + 3 times daily 500mg fo 5 days	quest Prot	5 days	Counts of AEs
Wen 2017	Taiwan	<u>N</u> : 9,793 adults <u>Age range</u> : >20 years	NSAID, No NSAID	Pain and fever relief	Dosage: n.r. Application: n.r.	Case- Crossove	Cases: 7 days	Risk of myocardi infarction
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99				BMJ Open	Medication details			
Study ID	Country	Population	Intervention & comparison	Indication for use	Medication details	Study design	Follow-up	Outcome
		<u>Mean age</u> : 72.3 years at diagnosis <u>Disease</u> : Acute respiratory infection (ARI			Frequency: n.r.	r Study		
Wen 2018	Taiwan	<u>N</u> : 29,518 adults <u>Age range</u> : > 20 years <u>Mean age</u> : 73.4 years <u>Disease</u> : 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. Solution: Dosage: 1) Celecoxib 200 mg		Cases: 7 days	Risk for ischemic and hemorrhagic stroke
Weckx 2002	Brazil, Colombia and Mexico	<u>N</u> : 357 adults <u>Age range</u> : ≥ 18 years <u>Mean age</u> : Celecoxib once daily: 32 Celecoxib twice daily: 31 Diclofenac: 32 <u>Disease</u> : Viral pharyngitis	Celecoxib, Diclofenac	Symptom relief	Dosage: 1) Celecoxib 200 mg 2) Diclofenac 75 mg <u>Application</u> : oral <u>Frequency</u> : 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	<u>N</u> : 47 children and adults <u>Age range</u> : 17-20 years <u>Mean age</u> : n.r. <u>Disease</u> : Influenza	Aspirin, Amantadine		Dosage:Aspirin:325 mgAmantadine 1:100mgAmantadine 2:100mgApplication:OralFrequency:For 5 daysAspirin:10 dailyAmantadine 1:1 dailyAmantadine 2:1 daily	RCT	7 days	Count of AEs: Medication side effects

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

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10. Effects	s on primary outco	mes reported by s	tudies included in the evide	nce synthesis
Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
Comparison	of NSAID use with no	NSAID use: Effects on	mortality	- mber 20
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 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 adult with H1N1 influenza are unclear. The confidence interval of the effect estimate is large, and includes the possibility of positive, null or negative effect.
NSAID use v	rs. no NSAID use: Effec	ts cardiovascular ever	nts	bmjops
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 associate with a higher odds ratio for ischemic streate 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 wi ARI on risk for ischemic stroke is unclear. The confidence intervals include the
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			BMJ (Dpen Narrative description Narrative description
Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
			= 1	စ possibility of a positive, null or negative နေရြင်း. ရွိ
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 associa 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, c) individuals without an ARI not exposed to NSAIDs. Confidence intervals overlap, indicating that the effect of NSAID in patients w ARI on risk for hemorrhagic stroke is unclear. The confidence intervals inclu the possibility of a positive, null or negative effect.
Multiple co	mparisons: Effects on	adverse event counts		
Multiple con Azuma 2010	mparisons: Effects on Zaltoprofen vs zaltoprofen vs placebo	adverse event counts Counts of severe adverse events (SAEs)		That study reports several mild adverse events, and explicitly states that severse adverse events occured (Quote "Three headaches, 2 odynophagias a 2 joint pain cases occurred in the 80-mg group. One odynophagia, 1 joint pain muscle pain, 1 glutamic oxaloacetic transaminase (GOT) increase and 1 lact dehydrogenase (LDH) increase occurred in the 160-mg group. All of these even were mild.")

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				Dpen Narrative description Parallel Parallel
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 pai were recorded in one patient treated with Novapirina and in five patients treate with Aspirin. No patient had to discontinue the treatment because of sid effects."
Boureau 1999	lbuprofen 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 SAE 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 (dyspepsia necessitating withdrawal of the atment and 1 bitter taste) and 3 case 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 $\frac{2}{3}$ verse experiences reported was rate 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 series adverse event (SAE) occurred. patient was treated with aspirin plus PSE [pseudoephedrine]. The SAE was a and feeling faint after the fall." The study also notes that "[t]he investiga considered that the fall and the faint feeting were not related to the study dru No.
Gehanno 2003	Diclofenac potassium vs Paracetamol	Counts of SAEs	Diclofenac potassium 6.25 mg: O SAEs Diclofenac potassium 12.5mg: O SAEs Diclofenac potassium 25 mg: O SAEs Paracteamol: O SAEs	The study reports that the patients reperting any AEs did not differ significa between study groups. Additionally, they report that "[n]o patients had to withdrawn from the study because of an adverse experience. There were serious adverse experiences and no deates 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. complained of several kinds of adverse events including drowsiness (in three) thirst (in two) during the follow-up period, which was higher than the one pat in the placebo group (1.1%) with drowsings."
Graham 1990	Aspirin vs acetaminophen (paracetamol) vs ibuprofen vs placebo	Counts of SAEs	Not explicitly reported	The study does not report explicitly on \vec{sA} Es, but reports that "the aspirin gr experienced more side effects than the other groups. Five in the aspirin gr did not complete the full course of medication, because of tinnitus in all 5 ca and gastrointestinal symptoms in 1 of those; they stopped on days 3 and Despite stopping medication, these valuateers continued to participate 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 w reported."
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Study ID	Intervention and control	Outcome	Effect estimate	Narrative description	990 on 1
Grunthal 2008	Acetylsalicylate (aspirin) + pseudoephedrin vs paracetamol + caffeine + chlorphenamine + vitamin C	Counts of SAEs	Not explicitly reported	The study reports that 4.8% of particip participants receiving aspirin reported si moderate severity". The most common "gastric pain, upper abdominal pain and	effects, which were "mostly of mild side effects in the aspirin group we
Hung 2017	Clarithromycin + naproxen + oseltamivir vs oseltamivir	Counts of SAEs	Not explicitly reported	The study notes that "no patient in ou drug-drug interaction." The study does 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 construction of the study reports that AEs were more construction or placeboostudy, a digestive haemmorrhage requires occurred in the amoxicillin-clavulanic actions of the study of the stud	groups. The only SAE in recorded in the groups of the only satisfies the second of the
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		
Milvio 1984	Nimesulide vs benzydamine	Counts of SAEs	Not explicitly reported	The study reports that "[n]imesulide wa patient suffered from moderate gastric p	
Nouri 1993	Nimesulide vs	Counts of SAEs	Not explicitly reported	The study notes that "[t]herapy with nig	<
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Study ID	Intervention and control	Outcome	Effect estimate	Narrative description	
	Naproxen			associated with adverse reactions. In the naproxen group, experienced episodic gastralgia of modeste intensity, one and the other on the eighth day of the apy. Laboratory p modified by either treatment."	starting on the third
Ottaviani 1993	Nimesulide	Counts of SAEs	Nimesulide: 10 SAEs out of 940 patients	The study reports that "[t]he drug was well tolerated, and o reported adverse effects, only 26 had to be withdrawn Physicians' assessments of therapeutic efficacy and tole were good in most patients". The SAB reported included sweating, flush, loss of appetite, vision disturbance, () [h dyspepsia, nausea, () [v]ertigo, () [r]a and urticaria."	from treatment. () rability of treatment d "[w]ater retention,
Schachtel 1988	Ibuprofen vs acetaminophen (paracetamol) vs placebo	Counts of AEs	Not explicitly reported	The study reports that "[n]o adverse effects were reporte The study provides only very little detail on whether a monitored.	
Schachtel 1991	Aspirin vs placebo	Counts of SAEs	Not explicitly reported	The study reports that "[o]f the 210 patients admitted to the (receiving aspirin) was discontinued after 1 hour because (nausea and vomiting) (). There were go other side effect the trial."	of an adverse effect
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 ev discontinued the study as a result of an adverse event."	vents, and no patient
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, death due to an AE. Overall, the incidence of Res was similar an groups."	

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				Narrative description
Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
			Celecoxib (low dose) + Placebo: 0 SAEs Placebo: 0 SAEs	9 November
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, a studymedication was well tolerated."
Sperber 1989	Pseudoephidrine + ibuprofen vs pseudoephidrine vs placebo	Count of SAEs	Not explicitly reported	The study notes that both drugs "weig generally well tolerated. No subject withdrew from the study due to adverse drug effects." The study mentions t following "possible adverse effects of geatment": "Lightheadedness, Difficu 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 t three cohorts. One volunteer in the naproxen group experienced gastrointestir symptoms after two doses of the drug, but after missing two doses, complet treatment without incident. Two gvolunteers receiving placebo h 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 symptomatic complaint on at least one occasion that they attributed to t medication. In the aspirin treatment group, the subjects took all tablets, but did not take all prescribed capsules. All bubjects took all medications the first days of the study. Six patients also had bleast one episode of insomnia, nause or tinnitus."
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Study ID	Intervention and control	Outcome	Effect estimate	Narrative description
Comparison	of ibuprofen with ac	etaminophen (paracet	amol): Effects on the rate of recor	nsultations Z
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 soldy reports 35/300 (11%) events in the paracetamol group, 58/295 (20%) in the bibuprofen group and 48/285 (17%) for the combined ibuprofen/paracetamol group. The adjusted risk ratio for the ibuprofen vs. the paracetamol group vars 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. Characto	eristics of and outcom	es reported in studies	included in the evidence mapping	g

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

Study ID	Study title	Study design	Partici-	Follow	Drugs	Disease / pathogen	Adverse	Reporting on adverse
			pants (n)	up			outeome reporting	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 experience reports that there weight there weight there adverse outsomes;	"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	Theo study explicitly reports on mile or moderate adværse outeomes, buto does noto meletion severe adværse outeomes;	"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 paracetamo 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 expansion of the study reparts severe adverse outgoomes; 	"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 feven 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	"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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							noto mention severe adverse outcomes;	tests were observed with e 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 expective reports on mile or moderate adværse outcomes, but does not meation severe adværse outcomes;	"Twelve children had mild effects: five of these were in Placebo group (nau abdominal pain, and cutaneous rashes), three these were in acetaminophen group (nau and five of these were in ibuprofen group (nausea abdominal pain). No other effects were repo Treatment was n interrupted because of 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 expectly reports that there were no adverse outcomes (without specifying the severity);	"There were no rele adverse effects observed du treatment or significant cha in the haematological profi 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 Dexibuprofen	vs.	Fever due to URTI	Theo study explicitly reports that there weee no sevare adverse outcomes;	"A total of 84 adverse events in 64/263 patients were reported Adverse events included vomiting, diarrhea, abdomina 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 of major sequalae."
Erlewyn- Lajeunesse 2006	Randomised controlled trial of combined paracetamol and ibuprofen for fever	RCT	123	1hour	Paracetamol Ibuprofen vs. Both	vs.	Fever	The study expective reports on mile or moderate adverse outcomes, but does not meetion severe adverse outcomes;	One child experienced a rapid temperature drop from 39.5°C to 37.7°C in one hour. She wa 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 suffe 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 Paracetamol	+ VS.	Fever due to: Upper RTI, Lower RTI, Gastrointestinal infection, Upper UTI, Soft tissue Infection, Otitis, Other	The study experts that there weee no severe adverse outgomes;	"Nineteen patients (9.5% experienced a total of 19 adverse events, 10 of them in the ibuprofen-arginine group and 9 following paracetamo 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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							990 on 19 Nove	neutropenia prior to the fi intake of paracetamol and the was consequently considered unrelated to the stu 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 outgomes; from http://bmjop	"A total of 18.4% (21/114) subjects reported 1 or mo adverse events; none we classified as serious. [] Dru related adverse events, that those that were classified by th investigator as definited probably, possibly, or unknown relationship to stud drug, were reported by 13.2 (15/114) of subjects (data n provided). All but 1 adver- event (cough increased) w 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 expanding study reports that there were no adverse outcomes (without specifying ther severity);	"No adverse reaction abnormal physical findings of abnormal laboratory resul attributable to eithe nimesulide or paracetam 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 expricitly reports on mile or moderate adverse	"Adverse reactions were seen the form of epigastric pain ar vomiting in one patient nimesulide group and thre patients in paracetamol group
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							severe	
							adværse	
							outŽomes;	
ladas 2011	Premarketing Surveillance of	Safety study,	490	7 days	Ibuprofen	Fever	The study	"Adverse reactions we
	Ibuprofen Suppositories in	uncontrolled			suppositories		exp∰citly	reported in 8 patients (1.63
	Febrile Children						reperts on	95% confidence interval = 1.7
							mil <u>∯</u> or	3.25). The most comm
							mogerate	adverse event was diarrhea:
							adværse	children (0.8%, 95% confiden
							out g omes,	interval = 0.24-2.2) had diarrh
							bută does	immediately after t
							not	administration of the drug. The
							mention	children developed a rash,
							severe	child had shivering, and 1 ch
							adverse	had rectal burning af
							outeomes;	suppository administration."
lay 2008	Paracetamol plus ibuprofen	RCT	156	5 days	Combination of	Fever	The study	Parents recorded adver
-	for the treatment of fever in				paracetamol and		explicitly	effects. "The most comm
	children (PITCH): randomised				ibuprofen vs.		reperts	adverse effects were diarrho
	controlled trials				Paracetamol vs.		severe	and vomiting, which we
					Ibuprofen		adv≩rse	equally distributed betwe
							out c omes;	groups. The overall number
								children experiencing adver
							20	events was, however, too sm
							124	to make meaning
							by	comparisons betwe
							gu	treatments. Five children we
							est	admitted to hospi
							Pr	(constituting serious adver
							ote	events)": PCM group:
							cte	ibuprofen group: 3, PCM p
							17, 2024 by guest. Protected by	ibuprofen group: 1 child.
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-	ayawar- dena 2017	Antipyretic Efficacy and Safety of Ibuprofen Versus	RCT	333	8 hours	lbuprofen vs. Acetaminophen	Fever	Theo study expicitly	"In total, 7.5% of patients in each treatment group had AEs.
5 6 7 8 9 10 11 12 13 14 15		Acetaminophen Suspension in Febrile Children: Results of 2 Randomized, Double-Blind, Single-Dose Studies				Acetaminophen		reports on mile or moderate adværse outeomes, bute does not meation severe adværse	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
16 K 17 1 18 1 19 20 21 22 23 24 25 26	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	outgomes; The study exparts that there were no adverse outcomes (without specifying the severity);	"In this single-dose study no side-effects were observed with either drug."
27 28 29 30 31 32 33 34 35 36 37 38 39					1	1	<i>h</i>	April 17, 2024 by guest. Protected by copyright.	
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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)	Theo study exposicitly reports that there were no adverse outeomes (without specifying theo severity);	"No adverse reaction abnormal physical findings, abnormal laboratory resinattributable to either ibupro or acetaminophen w 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 expansion of the study reparts severe advise outen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.	"Adverse events were report for 54 of the 100 patients, we most (97%) being classified mild to moderate in sever [] There were no deater ported in this study. The were no deater four (4%) subjects whom six serious advected whom six serious advected for serious adverse events; with pancreatitis and hepater and one with cardiac arrest is pneumothorax. In acetaminophen group, two (subjects experienced for serious adverse events; pleater of the serious adverse events were deement is the opinion of an independent of the serious adverse events were deement is presented to either intravent is presented to either is presented tother is presented tother is presented tother is prese

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Kim 201	1.3 Dexibuprofen for fever in children with upper respiratory tract infection	RCT	260	4 hours	Dexibuprofen (two different doses) vs. Ibuprofen	URTI	mjopen-2020-040990 on 19 November 2020. Downloaded from study The experience of the study representation on April 17, 2024 by adv come of the sevence of the	data safety monitor." "There were no signific differences in number of experienced (P = 0.98), model were there differences number of patie experiencing AE in each grown (DEX 1, n = 33; DEX 2, n = control, n = 35). When AE we classified according to sever (grades 1–5; data not shown there were no differences severity between the th groups. Of the 159 AE, all for three were grade 1 or 2. these three, two were fever a
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	C They study explicitly reparts on mile or moderate adverse	one was coughing." "During the study period, (21%) of all patients had symptoms includ diarrhea, flatulence, eme decreased appetite, epigast pain, nausea, headache, a
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					BMJ Open		njopen-2	
							mjopen-2020-0409900 does	
							not B metion severe adværse outeomes;	insomnia. These symptoms of not prevent any of the patien from taking the stur- medications. There were a differences between groups the incidence of any of the 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 expficitly reports on mile or moderate adverse outcomes, but does not mettion severe adverse outcomes;	"As far as the monitoring other ADR was concerned, on a few adverse effects namel epigastric pain, vomiting we encountered and on comparin it in different groups, r 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 expected study reports on mile or moderate adverse outcomes, buton severe adverse adverse outcomes;	"One patient develop hypothermia 4 h followi injection of diclofenac sodium "no asthmatic attacks occurra in the emergency room duri the observation" "Two patients with a history asthmatic bronchitis h wheezing" "there were no reported allerg reactions"
Luo 2017	Alternating Acetaminophen and Ibuprofen versus Monotherapies in	RCT	474	24 hours	Acetaminophen + ibuprofen vs. Acetaminophen	Febrileillness(duetosuppurativetonsillitis,URTI,	The study exponential reports on	"No obvious toxicities we observed" "Asthma": 2/157 in ibuprof
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3 4 5 6 7 8 9 10 11 12 12		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)	mileo or moderate adverse outeomes, bute does note metion sevore adverse outeomes;	group vs 0/156 in paracetamol and 0/158 in alternating group"
13 14 15 16 17 18 19 20 21 22 23 24 25 26	Marriott 1991	A dose ranging study of ibuprofen suspension as an antipyretic	RCT	93	12 hours	Ibuprofen (4 different doses)	Fever	The study expective reports on mile 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."
27 28 29 30 31 32 33 34 35 36 37 38 39	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 experies reperts severe adverse outbomes; Protected by	"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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					BMJ Open		mjopen-2020-0	
						septic arthritis, tracheitis, septicaemia	mjopen-2020-040990 on 19 Novemb	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 expected 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 experises on mile or moderate adverse outgomes, buto 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 mile or moderate adverse outcomes, bute 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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							metion severe adverse outgomes;	
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 expective reports that there were no severe adverse outcomes; de	"Safety evaluations at 1, 4 h after administration was good or very good by par investigators and childre more than 90% of the case both paracetamol and plac No serious adverse ev occurred. Four adverse ev were observed in 4 pati bronchitis and rash in ketoprofen lysine salt g diarrhoea and cough in 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 experts on mile or moderate adverse outcomes, but does not mention severe adverse outcomes;	"In this study, more adv events were observed naproxen than nimesulide." Most gastrointestinal (4 nimes recipients and 13 napr recipients [p < 0.05, Chi ² -t "Several naproxen recip reported more than 1 adv event [] Furthern urinalysis revealed a signif (p = 0.04) increase proteinurea for patients tree with naproxen compared those treated with nimesuli
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 they there	"None of the patients in a the groups had a drug-re adverse event or serious ill Mild elevation in levels of
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					and ibuprofen	Viral illness	ve@re adv@rse outdomes; ovember 2020. Download tried	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 expective reports on mile 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 outgomes st. Potential The study	"No significant between-group differences were observed with respect to adverse events of 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	Theo study expericitly	"No side effects from the drugs were seen in this series of

of 99					BMJ Open		mjopen-202	
					Aspirin vs. Paracetamol vs. Aminophenazone	infection	mjoppen-2020-04090rts repoorts that there were no adverse outcomes	patients."
Ugazio 1993	Clinical and pharmacokinetic study of nimesulide in	RCT (not blinded)	100	up to 9 days	Nimesulide oral suspension vs.	Acute URTI and fever	(without specifying the severity) The study expective	"there were no drug-related adverse events recorded"
	children				Paracetamol		reports that there were no adverse outcomes (without specifying the severity);	
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 wee 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 ²⁴ 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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								-04099 adverse	were [two] gastrointestin
								out <u>a</u> omes,	complaints (acetaminopher
				l				but does	exanthemas [ibuprofen:
								not _z	acetaminophen: 2], insomr
				l				mention	(ibuprofen), and hypotherm
								seväre	[ibuprofen: 2, acetaminophe
								adværse	1]."
				 				outcomes;	
/auzelle-	Antipyretic efficacy of	RCT	55	48 hours		icid	Fever	The study	"Five (9.1%) children h
ervroedan	tiaprofenic acid in febrile				vs. Placebo			exp∰citly	vomited during the six ho
.996	children							rep≦rts on	period after dosing: 3 in t
								mil <mark>a</mark> or	[placebo] group, and 2 in the
				l				moderate	group" [] "No major si
								adværse	effect was reported by t
								outeomes,	parents during the stu
								but <mark></mark> does	period"
								not	
								mention	
								severe	
								adværse	
								outgomes;	
'auzelle-	Equivalent antipyretic activity	RCT	116	2-4 days		vs.	Fever	The study	"Two children vomited duri
ervroedan	of ibuprofen and paracetamol				Acetaminopher	۱		explicitly	the study (1.7%), both of who
997	in febrile children							reports on	had received paracetamol."
								mil <mark>æ</mark> or	
				l				moderate	
								adverse	
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'yas 2014	Randomized comparative trial	RCT	99	4 hours		vs.	Upper respiratory	The study	"No serious or severe adver
	of efficacy of paracetamol,	l	<u> </u>	L	Ibuprofen	VS.	infection, lower	expericitly	events were noted in any of t
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99					BMJ Open		open-2	
							mjopen-2020-040990rts that there	
	ibuprofen and paracetamol-				Combination	respiratory	reports	groups. [] In the ibup
	ibuprofen combination for					infection, viral	that there	group, three patients out o
	treatment of febrile children					illness, bronchiolitis	were no	nuu experienceu une uu
							sev g re	events; one had nausea,
							adverse	abdominal pain and one
							outgomes;	maculopapular skin rash. A
							er 2	three adverse events were
							020	with a possible relationsh treatment. In the combin
								group, four patients out of
							OWI	had experienced the adv
							er 2020. Downloaded from http://bmjop	events. One patient
							lder	vomiting, which was mild
							d fro	doubtful relationship
							m	treatment. Two patients
							http	abdominal pain and one pa
							0://b	had a skin rash, which
							mj	mild with a possible relation
		D.07				-		to treatment."
Walker 1986	Comarative Efficacy Study of Chewable Aspirin and	RCT	46	4 hours	Aspirin vs.	Fever	The study explicitly	"Adverse effects were observed with either drug."
1900	Acetaminophen in the				Acetaminophen		reports	observed with either drug.
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Walson	Ibuprofen, acetaminophen,	RCT	118	48 hours	Ibuprofen	Fever	The study	
1989	and placebo treatment of febrile children				suspension vs.		exp#icitly reparts on	adverse experiences
					Acetaminophen elixir vs.		mil o or	
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							outcomes, butg does not does n	5 mg/kg ibuprofen, 6 of the 2 who received 10 mg/k ibuprofen, 6 of the 33 wh received 20 mg/k acetaminophen, and 2 of the 3 patients who received placebo.
Walson L992	Comparison of Multidose Ibuprofen and Acetaminophen Therapy in Febrile Children	RCT	64	48 hours	Ibuprofen vs. Acetaminophen	Fever	The study expericitly reports thas there weae no severe adverse outsomes;	Six children were withdraw from the study, two because of dosing errors, three because of hypothermia (temperature of less than 35.6°C; all three patients were in th acetaminophen group), and on because of gastrointesting distress (ibuprofen group). "N adverse effects of greater tha moderate severity wer 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 expective reports on mile or moderate adverse outeomes, but does not severe adverse outeomes;	One child had transier hypothermia and profuse nigh sweats due to pulmonar tuberculosis and a second chil had a transient drop temperature below 36.1°C
Nong 2001	Antipyretic effects of dipyrone versus ibuprofen versus acetaminophen in	RCT	628	14 days	Dipyrone vs. Acetaminophen vs. Ibuprofen	Fever	The study explicitly reports on mild or	"Most of the adverse even were gastrointestinal in nature such as vomiting and diarrhe Of the total adverse even

Page 91 of 9	99					BMJ Open		mjopen-2020-040	
2 3 4 5 6 7 8 9 10		multinational, randomized, modified double-blind study						moderate adverse outeomes, butz does note mention severe adverse	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
14 15 16 17 18 19 20 21 22 23 24 25	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	outeomes;	the incidence of adverse events." "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."
26 27 28 29 30 31 32 33 34 35 36 37 38 39	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	outeomes; The study experts on mild or moderate adverse outeomes, but does not meation severe adverse outeomes;	"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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12. Sub-group analyses (table s1)

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

Outcomes	Impact1	№ of participants (studies)	Certainty of the evidence (GRADE)2
1. Parenteral NSAIDs	0,		
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-pare	nteral 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)	
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)	
3. Low dose non-parer	nteral 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)	
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)	
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)	
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 LC

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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)	
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)	
7. Coxibs	0		
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 LO
8. NSAIDs other than C	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)	⊕⊖C VERY LO
9. More than one NSAI	Ds		
Myocardial infarction Acute respiratory infection Follow-up: exposure in case period (7d prior to event) were compared to exposure of patients	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)	⊕⊖C VERY LO

Explanations

¹All 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. ²All 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 for oper terien only 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

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).

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)	⊕⊕⊕⊕ нісн		
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 ♭		
Hospitalization for acute renal failure, anaphylaxis Follow-up: 4 weeks	Lesko 1995 O events in either group	83915 (1 RCT)	⊕⊕⊕⊕ нісн		
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 ♭		
Hospitalization for asthma Follow-up: 4 weeks	Lesko 1995 Relative risk of hospitalization for asthma: 0.92 (95% Cl: 0.56- 1.52)*	83915 (1 RCT)	⊕⊕⊕⊖ MODERATE ♭		
*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

Explanations

- a. Downgraded evidence by 1 level for study limitations: concerns for incomplete outcome reporting.
- b. Downgraded evidence by 1 level for imprecision. tor peer review only

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PRISMA 2009 Checklist

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1 2 3	PRISMA 20	009	Checklist 2020-0	
4 5 6	Section/topic	#	Checklist item	Reported on page #
7	TITLE		197	
8 9	Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
10	ABSTRACT	·	B B B e	
11 12 13 14	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
15	INTRODUCTION			
16 17	Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
18 19	Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, in Provide an explicit statement of questions being addressed with reference to participants, in Provide and study design (PICOS).	5
20	METHODS		tp://	
22 23	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
24 25 26	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
27 28	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
29 30 31	Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
32 33	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
34 35 36	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
37 38	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
39 40 41	Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
41	Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
43	Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including ne asures of consistency (e.g., I ²) for each meta-analysis.	7



PRISMA 2009 Checklist

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1 PRISMA 20)09	Checklist Page 1 of 2			
3		Page 1 of 2			
5 6 7 7	#	Checklist item	Reported on page #		
8 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		
10 Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7		
13 RESULTS		20.			
14 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		
17 17 Study characteristics 18	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		
¹⁹ 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		
20 21 Results of individual studies 22	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summare data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9		
²³ Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n.a.		
24 25 Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9		
²⁶ Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n.a.		
28 DISCUSSION		9 9			
29 30 31	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		
32 Limitations 33	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		
³⁴ Conclusions 35	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15		
37 38 Funding 39	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		
40					

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.
 43 For more information, visit: www.prisma-statement.org.
 44

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