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Echinacea for the prevention and treatment of upper respiratory tract infections: A systematic review and meta-analysis

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ABSTRACT

Background: Echinacea preparations are commonly used to prevent and treat upper respiratory tract infection.
Objectives: To assess current evidence for the safety and efficacy of echinacea containing preparations in preventing and treating upper respiratory tract infection.
Data sources: MEDLINE, EMBASE, CAB extracts, Web of Science, Cochrane DARE, clinicaltrials.gov and the WHO ICTRP – 1980 to present day.
Eligibility criteria: Randomised double-blind placebo-controlled trials using an echinacea preparation to prevent or treat upper respiratory tract infections.
Participants and interventions: Participants who are otherwise healthy of any age and sex. We considered any echinacea containing preparation.
Study appraisal and synthesis methods: We used the Cochrane collaborations tool for quality assessment of included studies and performed three meta-analyses; on the prevention, duration and safety of echinacea.
Results: For the prevention of upper respiratory tract infection using echinacea we found a risk ratio of 0.78 [95% CI 0.68–0.88], for the treatment of upper respiratory tract infection using echinacea we found a mean difference in average duration of −0.45 [95% 1.85–0.94] days, finally for the safety meta-analyses we found a risk ratio of 1.09 [95% CI 0.95–1.25].
Limitations: The limitations of our review include the clinical heterogeneity – for example many different preparations were tested, the risk of selective reporting, deviations from our protocol and lack of contact with study authors.
Conclusions: Our review presents evidence that echinacea might have a preventative effect on the incidence of upper respiratory tract infections but whether this effect is clinically meaningful is debatable. We did not find any evidence for an effect on the duration of upper respiratory tract infections. Regarding the safety of echinacea no risk is apparent in the short term at least. The strength of these conclusions is limited by the risk of selective reporting and methodological heterogeneity.
Implications of key findings: Based on the results of this review users of echinacea can be assured that echinacea preparations are safe to consume in the short term however they should not be confident that commercially available remedies are likely to shorten the duration or effectively prevent URTI. Researchers interested in the potential preventative effects of echinacea identified in this study should aim to increase the methodological strength of any further trials.
PROSPERO ID: CRD42018090783.

1. Introduction

Acute infections involving the nose, sinuses, pharynx or larynx are collectively referred to as upper respiratory tract infections (URTIs). In 2015, the global acute incidence was estimated at 17.2 billion URTIs, and for US adults URTIs are amongst the most common reasons for seeking healthcare.[1,2] Preparations of the plant *Echinacea* have been traditionally used to prevent and treat URTIs and research continues into the plausible mechanism.[3,4] In 2012, echinacea was the most popular herbal dietary supplement used by US adults and annual sales in the US alone are estimated to be in the $10 - $100 million range.[5–7] Despite its widespread use, the safety and efficacy of echinacea is still

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debated in the literature with previous reviews and meta-analyses reaching differing conclusions.,[4,8–12] A number of double-blind placebo-controlled trials were registered between 2005 and 2013, which have yet to be published or included in any systematic reviews and existing reviews and meta-analyses include errors in their methodology and data extraction. For these reasons we decided to undertake a new systematic review to assess the current evidence from double-blind randomised placebo-controlled trials for the safety and efficacy of echinacea preparations in the prevention and treatment of URTIs.

2. Methods

We registered a systematic review protocol with PROSPERO; protocol ID: CRD42018090783. We included any randomised double-blind placebo-controlled trial using an echinacea preparation to prevent or treat URTIs. Trials conducted from 1980 to the present day in populations of any age were considered and we allowed both peer-reviewed and unpublished trial reports. We excluded any trials where patient populations were not otherwise healthy; for example, those suffering from asthma. We also excluded any trials not reported in the English language. We searched MEDLINE, EMBASE, CAB extracts, Web of Science, Cochrane DARE, clinicaltrials.gov and the WHO ICTRP. See Fig. 1 for an example search strategy adapted from searches performed in two previous systematic reviews [4,10]

We also reverse searched systematic reviews.[4,8–10] We contacted academics and study sponsors of registered trials where we were unable to find a report of the trial. Both reviewers independently screened the list of records by title and abstract to exclude any entries that were clearly irrelevant. Potentially relevant records were identified for full text review according to the eligibility criteria.

Data was extracted using a piloted form. At all stages of study selection and data extraction both reviewers worked independently, comparing their work on completion and resolving any differences by discussion. For each study we recorded the trial registration number (where applicable), the number, age and sex ratio of the experimental groups and details of the treatment and placebo preparations. The primary outcome for trials assessing the efficacy of echinacea in the prevention of URTIs was the number of individuals who experienced at least one URTI. The primary outcome for trials assessing the efficacy of echinacea in the treatment of URTIs was the mean duration of the URTI ± standard deviation (SD); we also extracted the median when it was reported in place of the mean. The primary outcome for the assessment of the safety of echinacea was the number of individuals who experienced at least one adverse event (AE). Risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias at study level.[13] For the binary outcomes (prevention and safety) we used the risk ratio (RR) summary measure. For the continuous outcome (duration) we used the mean difference (MD).

For the trials that did not provide data suitable for quantitative synthesis we wrote a short narrative summary of the results relevant to our review questions. Where quantitative data was available, we synthesised the results of the included studies by meta-analysis with the R language for statistical programming version 3.5.0 [14] using the "meta" package.[15] For all outcomes we discussed only the random effects model because of the considerable methodological heterogeneity in the included studies, however the fixed effects model is displayed for comparison. For the two binary outcomes we used the "metabin" function which uses the Mantel-Haenszel method for pooling and the DerSimonian-Laird estimator for tau^2. For the continuous outcome we used the "metacont" function which uses inverse variance weighting for pooling and also uses the DerSimonian-Laird estimator for tau^2. In all cases we assessed between-study heterogeneity using the I^2 statistic. For the safety meta-analysis we included studies that reported 0 adverse events in both groups using a continuity correction of 0.5, following the recommendations of Cheng et al 2011.[16]

We made the following calculations and assumptions to aid in the synthesis of data. For the Jawad study [17] we calculated the number of people to suffer at least one URTI from the total infections and the number of people to suffer recurrent infection. For the Hall study, [18] as in previous reviews, we treated the reported incidence as number of people suffering from at least one URTI as there was no mention of recurrent infection, we also digitised the bar chart to calculate the SD for the mean duration. For the Zhang study [19] we calculated the SD for the mean duration using the reported standard error (SE). In the Barrett 2002 study [20] the SD for the mean duration of URTIs was reported as the overall SD in both groups. We accepted this value for our meta-analysis as in previous reviews. For the Turner 2005 study [21] we pooled the results from three experimental groups (different extractions of echinacea), and for the Melchart study [22] we pooled the results from two experimental groups (different species of echinacea). There was significant ambiguity in the report of the Lindenmuth study [23] with the authors concluding that the mean duration of URTIs was shorter in the echinacea group but reporting data which contradicted this. We preferred to take the statement of results rather than the author's interpretation.

To assess risk of bias across studies we visually inspected funnel plots for asymmetry for each meta-analysis conducted. Where appropriate we applied the linear regression test for asymmetry. We also considered the risk of selective reporting and publication bias present in the literature.

As per our protocol we performed subgroup analysis of adults and children as well as two unplanned sensitivity analyses which we considered helpful for interpreting the results.

3. Results

3.1. Study selection

The process of study selection is detailed in Fig. 2. We identified 5183 records through electronic searches and an additional 12 through

Number	Search
1	Echinacea/
2	echinac*.tw.
3	coneflower*.tw.
4	("E. purpurea" or E. angustifolia" or "E. pallida".tw.
5	black sampson*.tw.
6	1 or 2 or 3 or 4 or 5
7	remove duplicates from 6
8	limit 7 to english language
9	limit 8 to human

Fig. 1. Example search strategy.

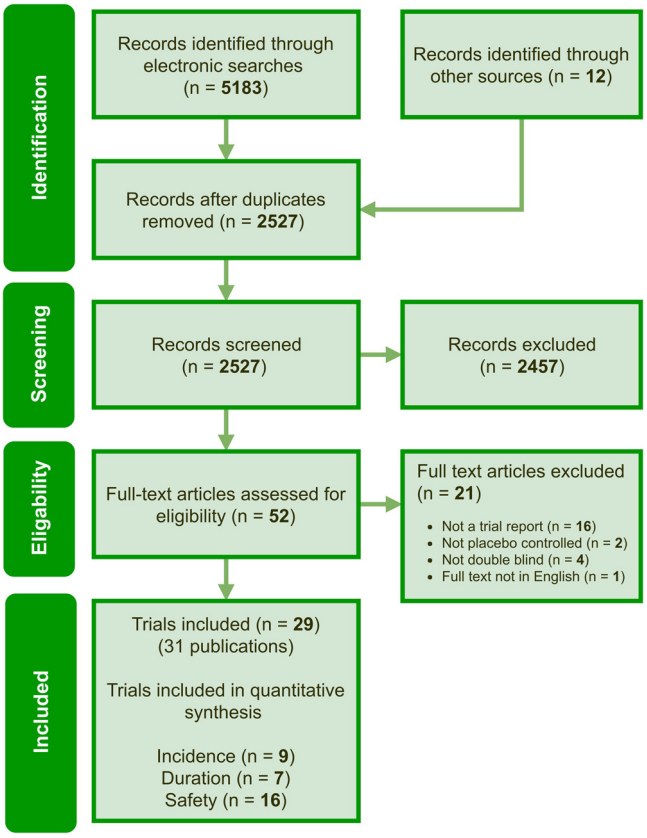

Fig. 2. PRISMA flow chart of study selection process.

reverse searching of previous systematic reviews. Twenty nine studies (in 31 publications) met our eligibility criteria.[17,18,27–36,19,37–45,20–26] Nine of these reported data for the prevention meta-analysis,[17–19,21,22,27,32,39,42] seven for the duration,[18–20,22–24,27] and 16 for safety.[17,19,37–39,41,42,45,20–23,25,27,32,36] Eleven studies did not provide quantitative data for a meta-analysis but met the eligibility criteria to be considered in a narrative summary.[26,28,44,29–31,33–35,40,43]

Three trials were identified as being potentially relevant but excluded after discussion between the reviewers. The trials by Berg [46] and Turner 2000 [47] were excluded as they were not described as double-blind. Although the abstract of the recent report by Rahmati [48] is written in English and provides an overview of the trial it is unclear as to whether the trial was double-blind, and the full text is in Persian.

3.2. Study characteristics

The characteristics of included studies are displayed in Table 1. The majority of trials were carried out in adult populations, two trials included participants of 12 years and older [24,32] and a further two focussed exclusively on paediatric participants.[27,45] Only two of the trials [21,39] used experimental virus inoculation with the rest using natural infection. In terms of the intervention; 16 of the trials reported using echinacea monotherapy; 14 with *E. purpurea* [17,18,38–40,44,19,25,26,30–32,34,37] two with *E. angustifolia* [21,29] and two with *E. pallidae* [28,41] and one trial [22] had separate groups for *E. angustifolia* and *E. purpurea*. Three trials did not specify which species of echinacea was used [23,43,45] and the remaining seven trials reported a mixed preparation treatment; 5 with *E. purpurea* and *E. angustifolia*[20,24,27,35,42] and two with *E. purpurea* and *E. pallidae*.[33,36] There were a wide variety of techniques used to prepare echinacea treatments utilising different parts of the plant, extraction methods and standardisation procedures.

3.3. Risk of bias within studies

Fig. 3A and B summarise the results of our risk of bias assessments. We rated five trials as having a low risk of bias in all categories.[24,30,33,36,40] Seven were rated as having at least one domain of high risk of bias,[19,22,23,29,35,37,38] and the remaining 17 had a mixture of low and unclear risk of bias across the domains.[17,18,34,39,41–45,20,21,25–28,31,32] The two weakest domains for the included trials were "incomplete data", mostly due to high dropout rates and "selective reporting" as several trials failed to report established endpoints

3.4. Results of individual studies

The results of individual studies extracted for quantitative synthesis are presented in Table 2.

3.5. Narrative summary

Many of the trials that met our eligibility criteria did not report data that could be included in our quantitative synthesis. We include a short narrative summary of the results of these trials with respect to our review questions. The prevention trials by Vemana [41] and O'Neil [37] did not report the number of people to experience at least one URTI, reporting URTI rates and sick days respectively; neither of these trials reported a significant difference between treatment groups. Eight trials provided a measure of URTI duration other than the mean ± SD.[17,32,34,37,38,40,41,43] The two largest of these were the Jawad [17] and Taylor trials, [40] both of which showed no treatment difference. In the case of the Jawad trial [17] we calculated the mean duration of URTIs as 4.5 days in both groups but could not calculate the SD. In the case of the Taylor trial [40] the median duration and 95% confidence intervals (CI) were reported as the same in both groups; 9 days (95% CI 8–10). Four smaller trials also reported durations that were unsuitable for quantitative synthesis but came to positive conclusions regarding the effect of echinacea on the duration of URTIs [34,38,41,43] with two more reaching negative conclusions. [32,37]

Trials by Taylor [40] and Brinkeborn [26] reported safety data but not the number of participants to suffer at least one AE. Taylor reported an increased risk of skin rash associated with the use of echinacea and Brinkeborn reported no significant difference between treatment groups. Many of the trials included data that is relevant to our review questions but did not lend itself to an easy or objective summary, for example, symptom severity scores, number of facial tissues used, surveys of treatment tolerability and other endpoints.

3.6. Quantitative synthesis of results

The results of our quantitative synthesis are shown in Fig. 4. Our meta-analysis of echinacea for preventing URTIs (Fig. 4A) gave a summary RR of 0.78 (95% CI 0.68-0.88), which shows a moderate and statistically significant reduction of the incidence of URTIs in the echinacea groups when the results are pooled. Study heterogeneity assessed by the I^2 statistic was moderate at 45%. The results of our meta-analysis for duration of URTIs (Fig. 4B) was a mean difference of -0.12 days (95% CI 0.93–1.22), in this case the results show that echinacea has essentially no effect on the duration of URTIs when the results are pooled. Study heterogeneity was high with I^2 at 97%. The results for our meta-analysis for safety (Fig. 4C) was an overall RR of 1.11, (95% CI 0.94–1.31) meaning there was no statistically significant difference between the two groups. Study heterogeneity was low with I^2 at 0%.

3.7. Risk of bias across studies

We produced funnel plots for each meta-analysis outcome, Fig. 5.

Table 1
Characteristics of Included studies.

	Pre-registration	Study design	Interventions [Brand]
Barrett, 2002 [20]	No	Treatment trial -Natural exposure Participants > 18 years	Treatment: *E. angustifolia* / *E. purpurea* (mixture) Placebo: Alfalfa
Barrett, 2010 [24]	NCT00065715	Treatment trial - Natural exposure Participants 12-80 years	Treatment: *E. angustifolia* / *E. purpurea* (mixture) Placebo: Same excipient material as treatment tablets
Barth, 2015 [25]	EUCTR2009-012640-17-FI	Treatment trial - Natural exposure Participants 18-65 years	Treatment: *E. purpurea* [**Kanjang**] Placebo: Sorbitol, hustenkräuter aroma, ginger extract, peppermint oil, dark syrup, benzoate and water
Brinkeborn, 1999 [26]	No	Treatment trial - Natural exposure Participants > 18 years	Treatment: *E. purpurea* [**Echinaforce**] Placebo: Not recorded
Cohen, 2004 [27]	No	Prevention trial - Natural exposure Participants 1-5 years.	Treatment: *E. angustifolia* / E. *purpurea* (mixture) [**Chizukit**] Placebo: "Indistinguishable from Chizukit by appearance, colour, or flavour"
Dorn, 1997 [28]	No	Treatment trial - Natural exposure Participants > 18 years	Treatment: *E. pallidae* Placebo: Coloured aqueous alcoholic solution
Galea, 1996 [29]	No	Treatment trial - Natural exposure Participants > 18 years	Treatment: *E. angustifolia* Placebo: Vegetable oil
Goel, 2004 [30]	No	Treatment trial - Natural exposure Participants 18-65 years	Treatment: *E. purpurea* **[Echinilin]** Placebo: Not recorded
Goel, 2005 [31]	No	Treatment trial - Natural exposure Participants 18-65 years	Treatment: *E. purpurea* [**Echinilin**] Placebo: "Contained similar ingredients, without the echinacea"
Grimm, 1999 [32]	No	Prevention trial - Natural exposure Participants > 12 years	Treatment: *E. purpurea* Placebo: Alcohol water solution
Hall, 2007 [18]	No	Prevention trial - Natural exposure Participants > 18 years	Treatment: *E. purpurea* Placebo: Sugar mixture
H.Von Zepelin, 1999 [33]	No	Treatment trial - Natural exposure Participants 18-70 years	Treatment: *E. purpurea* / *E. pallidae* [**Esberitox 5 N**] Placebo: "just the other ingredients"
Hoheisel, 1997 [34]	No	Treatment trial - Natural exposure Participants > 18 years	Treatment: *E. purpurea* [**Echinicin/ Echinaguard**] Placebo: Not recorded
Jawad, 2013 [17]	NCT01021995/EUCTR2009012297-12-GB	Prevention trial - Natural exposure Participants > 18 years	Treatment: *E. purpurea* Placebo: Alcohol drops
Kim, 2002 [35]	No	Treatment trial - Natural exposure Participants > 18 years	Treatment: *E. angustifolia* / E. *purpurea* (mixture) Placebo: Parsley juice and orange extract.
Lindenmuth, 2000 [23]	No	Treatment trial - Natural exposure Participants > 18 years	Treatment: Echinacea compound - species not recorded Placebo: Eaters digest herbal tea
Melchart, 1998 [22]	No	Prevention trial - Natural exposure Participants 18-65 years	Treatment: *E. angustifolia* / *E. purpurea* (separate trial arms) Placebo: Coloured ethanolic solution
Naser, 2005 [36]	No	Treatment trial - Natural exposure Participants > 18 years	Treatment: *E. purpurea* / *E. pallidae* Placebo: "Same inactive ingredients"
O, Neil, 2008 [37]	No	Prevention trial - Natural exposure Participants 18-65 years	Treatment: *E. purpurea* Placebo: Parsley
Schulten, 2001 [38]	No	Treatment trial - Natural exposure Participants > 18 years	Treatment: *E. purpurea* [**Echinicin/ Echinaguard**] Placebo: Not recorded
Sperber, 2004 [39]	No	Prevention trial - experimental inoculation Participants 18-65 years	Treatment: *E. purpurea* [**Echinicin/Echinaguard**] Placebo: "Identical in appearance, taste, and smell"
Taylor, 2003 [40]	NCT00029211	Treatment trial - Natural exposure Participants 2-11 years	Treatment: *E. purpurea* Placebo: Syrup
Thom, 1997 [41]	No	Treatment trial - Natural exposure Participants 18-40 years	Treatment: *E. pallidae* [**Kanjang**] Placebo: Vitamin C, Eucalyptic oil, Aqua purificata, sorbitol and preserving agent
Tiralongo, 2012 [42]	NCT00029211	Prevention trial - Natural exposure Participants 18-65 years	Treatment: *E. angustifolia* / *E. purpurea* (mixture) Placebo: Not recorded
Turner, 2005 [21]	NCT00032500	Prevention trial - Experimental inoculation Participants > 18 years	Treatment: *E. angustifolia* Placebo: mixture of alcoholic beverages, denatonium benzoate and tap water.
Vemana, 2016 [45]	NCT00231218	Prevention trial - Natural exposure Participants 1-6 years	Treatment: Echinacea - species not recorded Placebo: Chocolate flavoured syrup
Yakoot, 2011 [43]	No	Treatment trial - Natural exposure Participants Not stated	Treatment: Echinacea extract- species not recorded [**Immumax**] Placebo: Beeswax
Yale, 2004 [44]	No	Treatment trial - Natural exposure Participants > 18 years.	Treatment: *E. purpurea* Placebo: Lactose
Zhang, 2003 [19]	No	Prevention trial - Natural exposure Participants 18-65 years	Treatment: *E. purpurea* Placebo: Herb powder

We were unable to make a reasonable judgement of asymmetry for prevention and duration (Fig. 5). The funnel plots are not the same as the linear regression test, which is a statistical test of asymmetry. Funnel plots should normally be shown however a statistical test should only be conducted on meta-analyses of greater than ten trials.[49] The funnel plot for the safety meta-analysis looked symmetrical and the linear regression test for asymmetry was not significant (p = 0.4964).

Although we did not observe any asymmetry from the funnel plots, a symmetrical funnel plot does not exclude publication bias [50] and in addition we considered the direct evidence. We identified the following trial registrations that were relevant to our review questions but were never reported: clincialtrials.gov: NCT02003651; WHO ICTRP: ACTRN12612001199808, ISRCTN07988058, EUCTR2009-012640-17-FI. We contacted study sponsors and academics but could not obtain

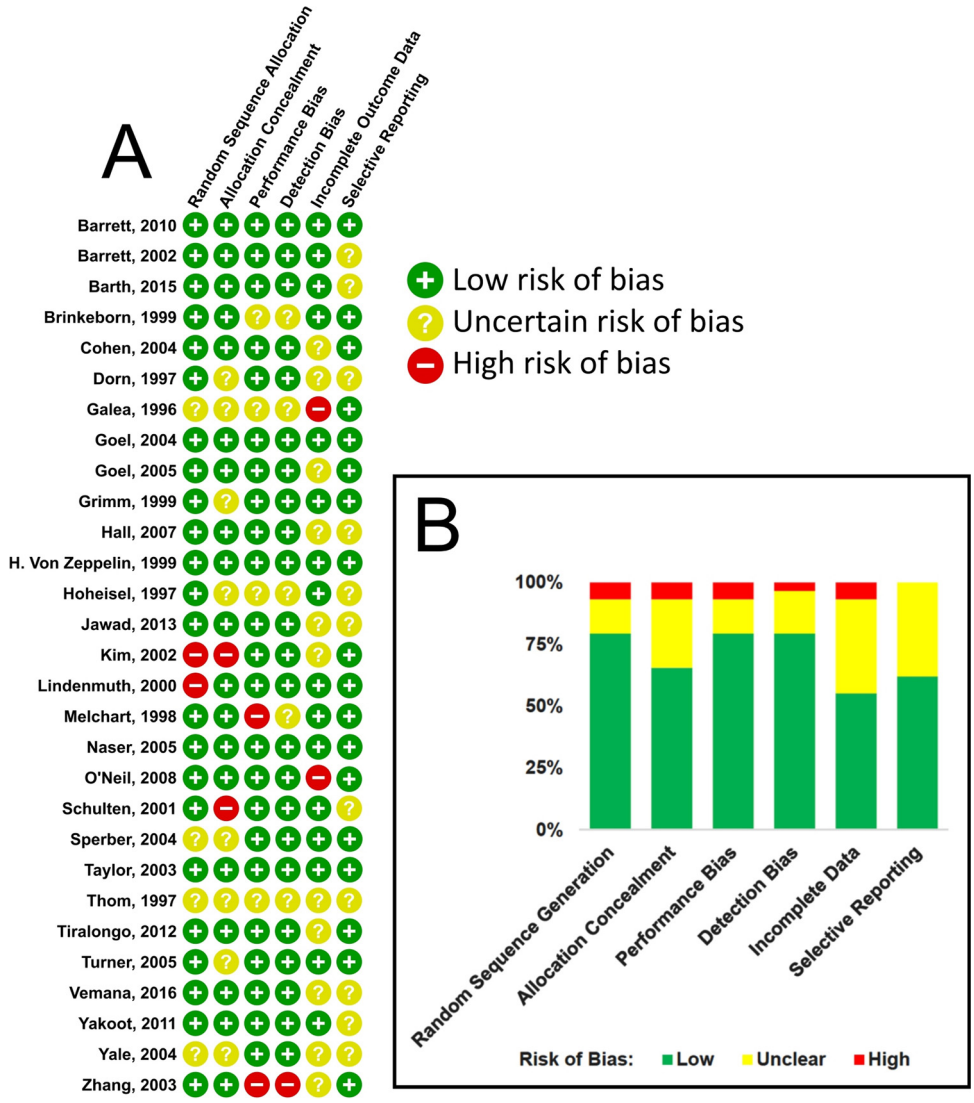

Fig. 3. Risk of bias results: **A:** Risk of bias table, Cochrane risk of bias tool assessed at study level. **B:** Risk of bias graph from data in **A**.

any results; this potential existence of unreported data creates a risk of publication bias.

Furthermore, there is a considerable selective reporting risk in the echinacea literature. For most of the trials we could not identify a registered protocol and many trials failed to report established outcomes, indicating the possibility of multiple comparisons and reporting bias. A clear example is the trial by Jawad[17] where the registered protocol did not define an outcome for efficacy with respect to either prevention or duration of URTIs. The authors reported total URTIs in each group and not the number of people to experience at least one URTI; the latter outcome being reported in many other trials previously.[19,21,22,27,32,39,42] The report also fails to state a mean or median duration of URTIs but instead reports the combined duration of URTIs in each group. Both missing outcomes can be calculated from the reported data and do not favour the use of echinacea (RR for prevention 0.87 [95% CI 0.71–1.07], Mean duration of URTI 4.5 days for both groups) although the paper concluded "a positive risk to benefit ratio" and a "significant therapeutic benefit". In many cases it is not possible to calculate or obtain values that have not been reported and we reviewed several papers where important outcomes that should have been reported were absent.

3.8. Additional analysis

As prescribed in our protocol we considered the results of adults and children separately. In the case of the prevention meta-analysis only the Cohen trial [27] focused on children and gave a RR of 0.60 [95% CI 0.51-0.69]. The remaining adult subgroup had a RR of 0.84 [95% CI 0.75-0.93] compared to the RR of all studies 0.78 [95% CI 0.68-0.88]. This also serves as a useful (unplanned) sensitivity analysis of the overall result to the Cohen trial as it is the only trial that reached significance and received the highest weighting in the pooled result. Although the Cohen trial reported the greatest effect size of all prevention trials, a recent replication by Vemana et al.[45] reported a negative conclusion. One interesting effect of removing the Cohen study from the meta-analysis is the lack of study heterogeneity in the remaining studies with the I^2 statistic at 0%. In the case of the duration meta-analysis no trials focused exclusively on children. We conducted an unplanned sensitivity analysis by excluding the Lindenmuth[23] trial because of the ambiguity in the report. With the Lindenmuth trial excluded the MD decreases to favour echinacea MD -0.73 days [95% CI -1.55-0.1] but the pooled result does not reach significance. In the case of the safety meta-analysis the trials by Cohen[27] and Vemana[45] were conducted exclusively on children, the subgroup analysis of these two trials gave a RR of 1.33 [95% CI 0.52–3.4] and the subgroup for adults was 1.08 [95% CI 0.94–1.24]. We also conducted an unplanned sensitivity analysis to the

Table 2
Results for quantitative synthesis.

	Incidence treatment	Incidence control	Events treatment	Mean duration treatment (SD)	Events control	Mean duration control (SD)	AEs treatment	AEs control
Barrett, 2002 [20]	NA	NA	69	6.27 (2.34*)	73	5.75 (2.34*)	8/73	7/75
Barrett, 2010 [24]	NA	NA	184	6.34 (3.31)	179	6.87 (3.62)	NA	NA
Barth, 2015 [25]	NA	NA	NA	NA	NA	NA	2/66	4/54
Brinkeborn, 1999 [26]	NA	NA	NA	NA	NA	NA	NA	NA
Cohen, 2004 [27]	85/160	150/168	138	1.6 (1.9)	308	2.9 (1.6)	9/160	7/168
Dorn, 1997 [28]	NA	NA	NA	NA	NA	NA	NA	NA
Galea, 1996 [29]	NA	NA	NA	NA	NA	NA	NA	NA
Goel, 2004 [30]	NA	NA	NA	NA	NA	NA	NA	NA
Goel, 2005 [31]	NA	NA	NA	NA	NA	NA	NA	NA
Grimm, 1999 [32]	35/54	40/54	NA	NA	NA	NA	11/54	7/54
Hall, 2007 [18]	7/18	7/14	7	3.4 (3.14)	7	8.6 (4.77)	NA	NA
H.Von Zepelin, 1999 [33]	NA	NA	NA	NA	NA	NA	26/131	23/132
Hoheisel, 1997 [34]	NA	NA	NA	NA	NA	NA	NA	NA
Jawad, 2013 [17]	112/355	131/362	NA	NA	NA	NA	177/355	172/362
Kim, 2002 [35]	NA	NA	NA	NA	NA	NA	NA	NA
Lindenmuth, 2000 [23]	NA	NA	48	4.33 (0.93)	47	2.34 (1.09)	0/48	0/47
Melchart, 1998 [22]	61/199+	33/90	61	8.0 (5.11)	33	8.7 (3.6)	28/199	11/90
Naser, 2005 [36]	NA	NA	NA	NA	NA	NA	0/63	0/31
O, Neil, 2008 [37]	NA	NA	NA	NA	NA	NA	2/28	2/30
Schulten, 2001 [38]	NA	NA	NA	NA	NA	NA	6/41	6/39
Sperber, 2004 [39]	14/24	18/22	NA	NA	NA	NA	2/24	4/22
Taylor, 2003 [40]	NA	NA	NA	NA	NA	NA	NA	NA
Thom, 1997 [41]	NA	NA	NA	NA	NA	NA	0/30	0/30
Tiralongo, 2012 [42]	31/72	43/76	NA	NA	NA	NA	4/85	1/85
Turner, 2005 [21]	73/149+	58/103	NA	NA	NA	NA	15/315	4/104
Vermana, 2016 [45]	NA	NA	NA	NA	NA	NA	0/49	0/54
Yakoot, 2011 [43]	NA	NA	NA	NA	NA	NA	NA	NA
Yale, 2004 [44]	NA	NA	NA	NA	NA	NA	NA	NA
Zhang, 2003 [19]	25/54	33/57	44	2.20 (3.12)	60	3.07 (3.64)	15/54	4/57

Incidence: Number of individuals to suffer at least one URTI/total group population. Events: Number of URTIs per group AEs: number of people in each group to suffer at least one adverse event/total group population.

+ Pooled incidence data for different treatments.

* SD given for the mean across combined groups.

Jawad[17] trial because of the large number of events reported and the high weighting of this result in our meta-analysis. When excluding the Jawad trial the RR was 1.28 [95% CI 0.93–1.75].

4. Discussion

4.1. Summary of evidence

When considering the use of echinacea in prevention of URTIs, none of the individual treatments assessed by the primary outcome reached significance, with the exception of the Cohen study.[27] When combining data from all studies the random effects model shows a small reduction in the risk of suffering from a URTI whilst under the treatment of echinacea, Fig. 4A. However the clinical heterogeneity limits the strength of meta-analysis in summarising these results. If this treatment effect is genuine, it is debatable whether it would carry over into a real world setting as a meaningful difference, where compliance is poor and echinacea preparations variable.[51]

In terms of using echinacea to shorten the duration of URTI, two trials significantly favoured echinacea and one the placebo. The summary measure showed no overall benefit, Fig. 4B. A significant body of research was unavailable for meta-analysis with a mixture of positive and negative results, however the two largest trials, which could not be included in the meta-analysis,[17,40] both gave significant negative results.

With respect to the safety of echinacea; despite the heterogeneity in reporting of AEs, it is likely that echinacea is safe in the short term. Only one of 16 studies[19] reached significance in the meta-analysis, finding a greater number of participants who suffered at least one AE the echinacea group. The overall RR was close to 1. Long-term results remain uncertain and, as shown by recent debate regarding gynecomastia caused by essential oils,[52] caution should be exercised in the face of uncertainty and limited benefits.

4.2. Differences between our review and existing relevant literature

The 2006 meta-analysis by Schoop and colleagues[10] focused on echinacea in the prevention of induced rhinovirus infection. In this review the Turner 2000[47] trial is described as double-blind however to the best of our knowledge this isn't the case. It isn't clear that double-blinding formed part of the eligibility criteria for their meta-analysis however by describing a more rigorous methodology than the researchers themselves the robustness of the meta-analysis result is overstated.

A 2007 review by Shah and colleagues[9] on echinacea in the prevention and treatment of the common cold includes a meta-analysis on duration data with several errors incorporated. For the Lindenmuth trial[23] the result was extracted as shorter duration in the echinacea group however the paper reports the opposite. For the Barrett 2002 trial[20] the result was correctly extracted (shorter duration in the placebo group) but the meta-analysis plots the opposite, as noted in a letter by Von Maxen and Schonenhoefer.[53]Recalculation of their meta-analysis using the same method, but the correct data gives a non-significant result with a MD of -0.61 days [95% CI -2.23 - 1.01] compared to that reported in the paper of -1.44 days [95% CI -2.24 - 0.64]. Furthermore, this review reports data from the Taylor 2003[40] trial as "mean duration" however the results are specified to be median. Finally the authors include results from the trial by Braunig[54] which recruited patients suffering from influenza, not the common cold as specified in their eligibility criteria.

We identified several data extraction problems in the 2014 review by Karsch-Volk and colleagues.[4] For the Jawad study[17] (the largest

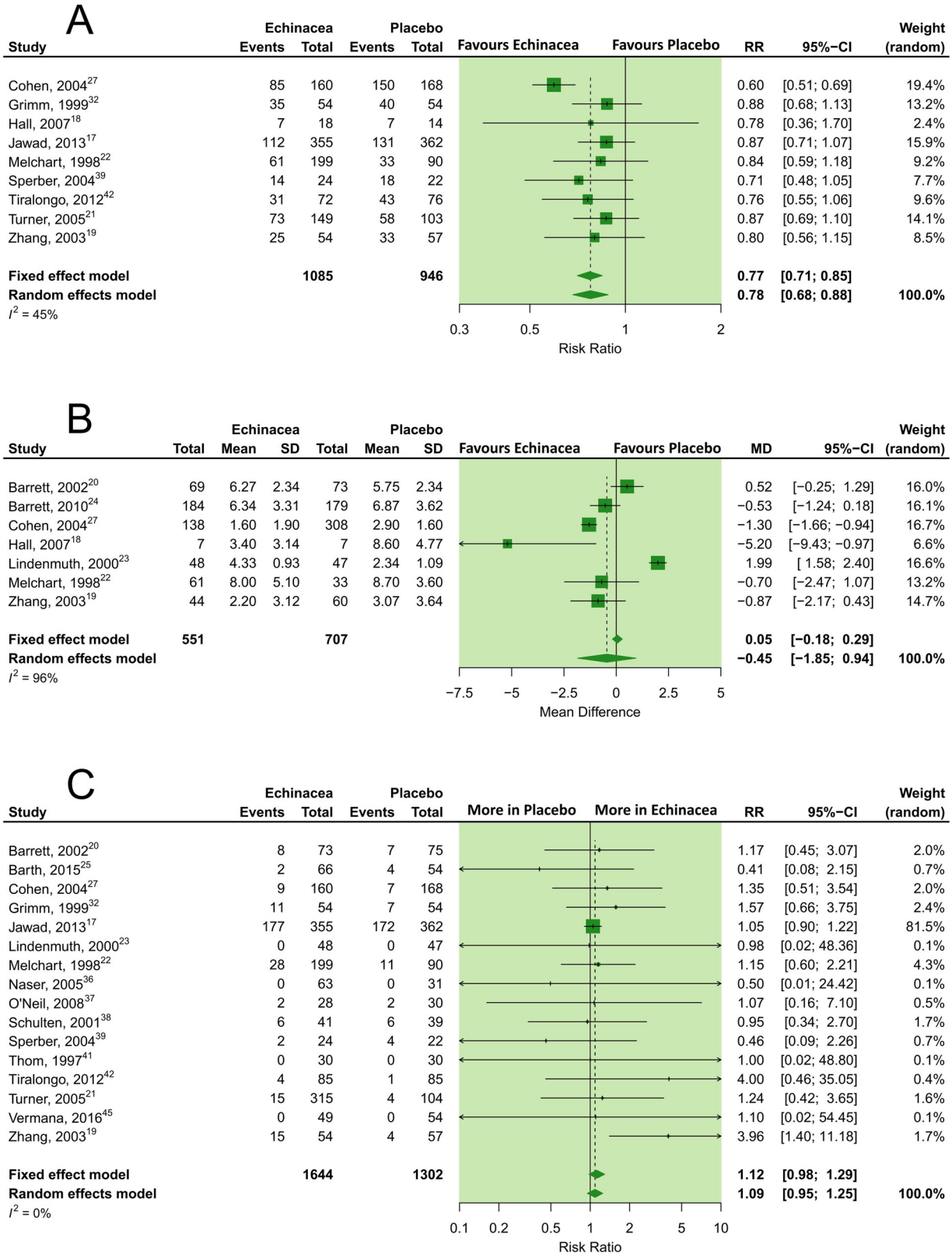

Fig. 4. Echinacea versus placebo forest plots of study results: **A:** Echinacea versus placebo for the prevention of URTIs, meta-analysis of the proportion of patients suffering at least one URTI, RR = risk ratio. **B:** Echinacea versus placebo, meta-analysis of the duration of URTIs, MD = mean difference. **C:** Echinacea versus placebo, meta-analysis of proportions for participants experiencing at least one adverse event, RR = risk ratio.

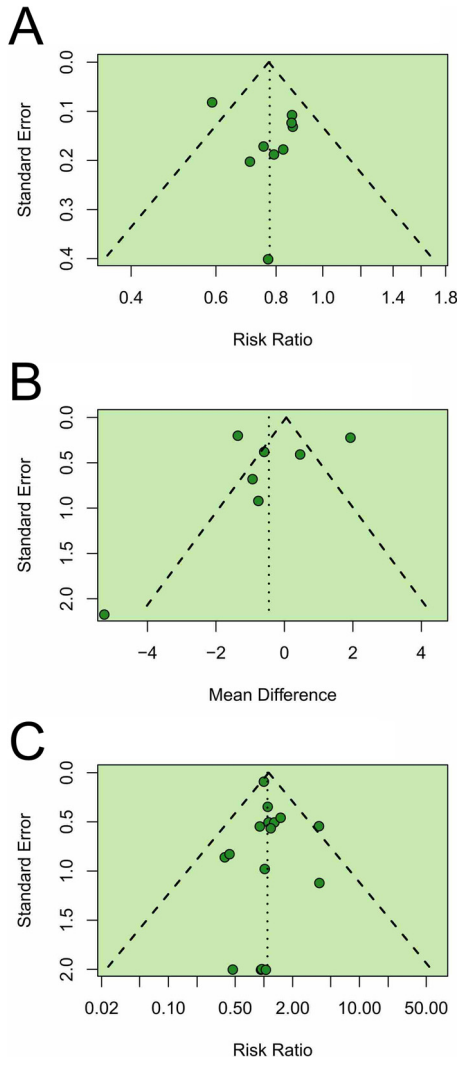

Fig. 5. Echinacea versus placebo funnel plots of study results: **A**: Funnel plot of studies investigating the prevention of URTIs. **B**: Funnel plot of studies investigating the duration of URTIs. **C**: Funnel plot of studies investaing the safety of echinacea.

double-blind prevention trial to date), both prevention and mean duration of URTIs (without SD) can be calculated from the data in the paper, but was excluded from this review. This review also describes the Turner 2000 trial[47] as double-blind without any obvious justification and incorporates the Lindenmuth duration data[23] into the meta-analysis with the treatment effects reversed. Finally the review reports data on prevention of URTIs from the O'Neill trial[37] but this data is not reported in the O'Neill paper and the review does not mention any contact with study authors.

Although not a systematic review; A 2015 paper by Schapowel and colleagues[8] reports two relevant meta-analyses on treating recurrent URTIs using echinacea, but includes two important methodological errors. Firstly, the count data of recurrent infections is treated as a dichotomous variable (see section 9.2.5.1 of the Cochrane handbook "Effect measures for counts and rates").[55] Secondly, in calculating risk ratios participants are included who were not at risk of a recurrent URTI as they had not suffered an initial URTI. In their second meta-analysis which investigated the use of echinacea in increased susceptibility groups different subgroups from the same trial were pooled causing pseudo-replication of the placebo arm; An overall risk ratio cannot be derived in this way and reporting one is misleading.[56] A recent systematic review and meta-analysis by Anheyer and colleagues[12] considered the effects of herbal medicines in treating respiratory tract infection in children. The authors identified the studies by Cohen[27] and Taylor[40] but due to their more restrictive search strategy did not identify the trial by Vemana.[45] The review by Anheyer and our own review reached similar conclusions regarding the lack of evidence for the use of echinacea in children with respiratory tract infections.

4.3. Limitations of this review

We made some adjustments to our protocol prior to data interpretation. For primary duration outcome we initially proposed to record "duration of clinical symptoms" but updated this to the mean and SD of the URTI so that we could perform a meta-analysis on this data. For the same reason we refined our primary safety outcome from "number and type of adverse events reported" to "number of people to suffer at least one adverse event". We dropped our planned subgroup analyses of "different preparations of echinacea" as we did not anticipate the large variety of treatments used in these trials, which defied any obvious subgrouping strategy; for example, it is not clear whether preparations containing the same species should be grouped together or if the extraction method or even the dose is more important. Clarifications notwithstanding, this is the first review on this subject to have registered any protocol.

This review was limited to double-blind randomized trials, excluding some evidence from studies with different designs. The search was also limited to English-language only, excluding some trials reported in German that may have been relevant to our review question. Despite this, we have reviewed the greatest number of trials yet and by restricting trial design we expect the quality of evidence to be greater.

Due to time limitations, we did not contact authors for additional data beyond obtaining a trial report. Some evidence that would have been relevant to our review questions might still be obtainable from study authors.

Although we opted to pool our results and produce a summary measure, in all instances methodological heterogeneity was significant, and this seriously limits the strength of any conclusion that can be drawn from the meta-analyses. As in previous reviews we also analysed duration data using the mean difference summary measure. However, informal testing suggests that the duration data sets are likely to be skewed limiting the usefulness of this technique. (See Cochrane handbook chapter 9.4.5.3 "Meta-analysis of skewed data").[57] It is perhaps because of this skewing of data that many trials reported the median duration instead of the mean.

4.4. Future research

Useful recommendations for any future research include the prior registration of a clear trial protocol in which all the primary outcomes are unambiguously defined. Clearer reporting of study results - for example following the CONSORT statement.[58] Standardisation of the treatment and placebo preparations used as well as effective disguising of the taste of echinacea with another strong flavour. Subsequent testing of participant and researcher blinding would also be beneficial. We identified compliance as a problem in our quality assessments, even simple measures such as pill counting would be desirable.

4.5. Conclusions

Whilst echinacea appears to be safe in the short term the claims that preparations of this plant can reduce the incidence or duration of URTIs remain to be convincingly shown. The statistically significant result in our meta-analysis for echinacea in the prevention of URTIs is diminished by the likely presence of selective reporting, publication bias and methodological heterogeneity of the included studies.

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