Appendix 1: Discussion of other interventions for the prevention and treatment of the common cold

Studies of other interventions mentioned in the sections "other interventions" of the main article and in this appendix frequently considered a host of outcomes (e.g., for nasal symptoms: rhinitis, sneezing, congestion, and nasal discharge), multiple scales for each outcome, varying cut-offs for relevance, different time frames (e.g., 1 d, 3 d, 5 d), and difficult-to-interpret statistics (standard mean difference). In these cases, we did our best to sum up the evidence without simply selecting one or two positive or negative outcomes.

What other interventions are effective for preventing the common cold?

Vitamin C

Vitamin C prophylaxis does not reduce the number of cold episodes for the average patient.[1] Despite the enthusiasm for mega-doses, limiting analysis to higher-dose trials did not improve the number of cold episodes either.[1] Although daily vitamin C results in a statistical reduction in the duration of colds (mean difference –9.1, 95% confidence interval [CI] –12.6 to –5.6), in actual time it translates to slightly less than one day, based on the average cold lasting 10 days.[1] Furthermore, the severity reduction of –0.12 (95% CI –0.17 to –0.07)[1] fails to meet standard criteria[2] of even a small change. There may be benefit in people under more physical stress (e.g., marathon runners or soldiers in subarctic environment), but this outcome is based on only five trials with 598 patients.[1] Overall, daily vitamin C cannot be recommended for prophylaxis against the common cold for the average patient.

Echinacea

Echinacea is available in a staggering variety of formulations with differing species (three species commonly used), plant parts, extraction method, stabilization with alcohol, concentration and dosing.[3] A Cochrane systematic review[3] identified two trials of echinacea with three comparisons for the prevention of the common cold. The active ingredients were *Echinacea purpurea* flowering parts in a juice of 22% alcohol as 4 mL twice a day, *E. purpurea* root extract in 30% alcohol as 50 drops twice a day, and *E. angustifolia* root extract in 30% alcohol as 50 drops twice a day. The Cochrane authors felt the variations did not permit pooling of trial data. None of the three comparisons showed statistical difference from placebo in preventing one or more infections, dropout due to adverse events or any adverse events.

Exercise

We found only one small RCT of a select population of 115 overweight or obese postmenopausal women that assessed exercise as prophylaxis against the common cold.[4] Concerns with this trial include unclear allocation, multiple analysis, self-reported outcomes in an unblinded study and conflicting results (colds decreased, but not overall upper respiratory tract infections [URTIs]). It is unclear whether exercise reduces the risk of the common cold.

Appendix to: Allan GM, Arroll B. Prevention and treatment of the common cold: making sense of the evidence. *CMAJ* 2014. DOI:10.1503/cmaj.121442.

Garlic

Garlic appears promising, but its use is supported by only one RCT of poor quality.[5,6] Therefore, the benefit of garlic for prophylaxis against the common cold is uncertain.

Homeopathy

We found three RCTs that examined the effect of homeopathic medicines on the prevention of URTIs in children aged 10 or less.[7–9] Two of the RCTs used placebo as the control, and neither found a significant difference in URTI events, days with symptoms or symptom scores.[7,8] The other RCT used a wait-list as the control group.[9] The homeopathy group versus the wait-list group had a reduction in the mean total symptom score (24 v. 44 points respectively, $p = 0.03$) and median number of days with symptoms (8 v. 13 days respectively, $p = 0.006$).[9] There were no differences in seeing a medical doctor, being prescribed antibiotics, or days that parents were off work.[9] Using an open, unblinded study relying on parent-assessed symptom scores, this study's results would be at high risk of bias.[9] Therefore, the present evidence is unclear and does not support the use of homeopathic medicines for the prevention of the common cold.

Vitamin D

Based on available evidence, vitamin D prophylaxis has no benefit in the prevention of the common cold. One RCT[10] that assessed vitamin D for the prevention of URTI (although not specifically the common cold) included a highly selected group of 164 volunteers from 400 male military recruits in the Finnish military. The proportion of participants with no days absent from duty was 51% for vitamin D versus 36% for placebo ($p = 0.045$). However, this benefit was no longer significant when adjusted for baseline risks such as smoking cessation (hazard ratio 0.71, 95% CI 0.43 to 1.15). None of the other 16 outcomes (e.g., symptoms, timing of missed work) were significantly improved. The recent VIDARIS RCT[11] randomly assigned 322 health care workers and students to vitamin D 200 000 units monthly for 2 months and then 100 000 units monthly thereafter for 18 months. The trial was well-designed and found no difference in number of URTI, the severity of URTI or consequences such as missed days of work. Studies of vitamin D supplementation for influenza prevention have conflicting results.[12,13]

What medications are effective for treating the common cold?

NSAIDs

The evidence for NSAIDs in the treatment of the common cold arises from a systematic review and meta-analysis.[14] NSAIDs had no effect on cold duration, overall symptom scores or the majority of respiratory symptoms. Pooled results of two studies suggested a reduction in the sneezing score (standard mean difference –0.44, 95% CI –0.75 to –0.12). This might be considered a small to moderate change in sneezing. However, other nasal symptoms (e.g., nasal obstruction, rhinorrhea) showed no effect; the reduced sneezing score may be a spurious result from multiple comparisons. Analgesic effects generally favoured NSAIDs, with a reduction in headache (standard mean difference –0.65, 95% CI –1.11 to –0.19), earache (standard mean difference –0.59, 95% CI –1.04 to –0.14) and likely muscle aches (standard mean difference –0.42, 95% CI –0.86 to

0.01), but not throat irritation (standard mean difference –0.01, 95% CI –0.33 to 0.30). Overall, NSAIDs are not effective for treating most symptoms of the common cold, but they can help with some of the associated aches and pains.

Acetaminophen

Data on acetaminophen (or paracetamol) in the treatment of the common cold are sparse. One RCT compared single doses of acetaminophen, acetylsalicylic acid (ASA) and placebo in 392 adults with febrile URTI of suspected viral origin.[15] Another RCT compared acetaminophen, ibuprofen and nimesulide in 90 children with febrile URTI. Both RCTs had methodologic concerns in the description of randomization and allocation concealment. Furthermore, both trials may not have represented the common cold, since adults generally do not have fever with the common cold[15] and 54% of patients in the pediatric study had bacterial infections.[16] In adults, a single 1000-mg dose of acetaminophen improved headache, aches and fever discomfort, from about 6 to 4 (on a 10-point scale) versus placebo ($p < 0.001$ for each).[15] Fever was also significantly improved versus placebo ($p < 0.001$). No difference between 1000 mg of ASA and 1000 mg of acetaminophen was observed for any outcome.[15] The pediatric RCT found little difference between ibuprofen and acetaminophen except for a slightly improved fever reduction at four hours with ibuprofen ($p < 0.001$) and slightly improved cough reduction with acetaminophen ($p < 0.05$), although the latter may be a spurious result from low numbers and multiple comparisons.[16] In meta-analyses[17,18] comparing ibuprofen and acetaminophen at equivalent doses for fever from various conditions, ibuprofen provided superior fever reduction (e.g., at four hours) (weighted-effect sizes 0.31, 95% CI 0.19 to 0.44).[17] Safety of ibuprofen and acetaminophen were equivalent, at least in pediatric populations.[17,18] Overall, acetaminophen appears to be more effective than placebo for fever and analgesic effects, but it is likely inferior to ibuprofen, at least for fever in pediatric populations.

Acetaminophen and ibuprofen together

The combination of acetaminophen and ibuprofen for fever was best assessed in the PITCH trial.[19] Hay et al studied children aged six months to six years with a fever (37.8°C to 41°C) who could be safely treated at home and randomly assigned them to either acetaminophen (paracetamol), ibuprofen or both. The dose of acetaminophen was 15 mg/kg every four to six hours and ibuprofen 10 mg/kg every six to eight hours.[19] They found acetaminophen plus ibuprofen was superior to acetaminophen alone for less time with fever in the first four hours (adjusted difference 55 minutes, 95% CI 33 to 77; $p < 0.001$) and the combination may have been as good as ibuprofen. For less time with fever over 24 hours, acetaminophen plus ibuprofen was superior to acetaminophen alone (4.4 h, 95% CI 2.4 to 6.3; $p < 0.001$) and to ibuprofen (2.5 h, 95% CI 0.6 to 4.4; $p = 0.008$). Combined therapy cleared fever 23 minutes faster than paracetamol alone but not faster than ibuprofen alone. No benefit was found for discomfort or other symptoms, although the statistical power was low for these outcomes. There was no difference in adverse effects. Over-dosing (more than the recommended doses per day) of each drug occurred in 6%–13% of children, and it is not clear whether the different dosing frequencies of the two drugs may have been a challenge for some parents.

Antibiotics

A meta-analysis and systematic review provided evidence regarding the use of antibiotics in the common cold.[20] The effect in reducing persistent symptoms lasting one to seven days was not significant (relative risk 0.95, 95% CI 0.59 to 1.51). Adverse events were significantly increased with antibiotic use (relative risk 1.8, 95% CI 1.01 to 3.21). The trial efficacy and adverse events results were inconsistent, reflected in the high heterogeneity (I^2 = 76% and 66%, respectively). Antibiotics offer no benefit in treatment of the common cold and increase harms.

For front-line clinicians, the battle to minimize antibiotic prescribing is a challenge, particularly because the presentation of URTIs overlaps that of other conditions such as otitis media, sinusitis, pharyngitis and even pneumonia. In conditions where clinicians were considering, but were uncertain about, prescribing an antibiotic for possible bacterial infection, delayed prescribing reduced filled antibiotic prescriptions from 93%–32%.[21]

What alternative or nonpharmacologic therapies are effective for treating the common cold?

Honey

In two trials, honey was found to improve 7-point sleep or cough scores about 0.5 better than dextromethorphan, which was 0.5 better than no treatment ($p < 0.005$).[22,23] In a third trial, three types of honey were compared with silan date extract (for similar taste and appearance to honey) over five different 7-point sleep or cough scores.[24] There were no differences between honey types, but each type of honey resulted in about 0.8 larger improvement on each scale than silan date extract ($p < 0.04$ or better).[24]

Nasal irrigation

Given the limited evidence and generally negative results, the effect of nasal irrigation on the common cold is uncertain. Evidence comes from a systematic review of saline or hypertonic saline delivered in drops in children and infants, or nasal irrigation in adults and children.[25] The three trials included in the review had important methodologic concerns such as poor randomization methods and unclear allocation concealment. In two pooled studies, there was no significant improvement in nasal symptoms at day 3 (standard mean difference –0.07, 95% CI –0.45 to 0.31). Most results were not significantly improved with nasal saline (hypertonic or isotonic). Use of antibiotics was unchanged, although one study found a reduction in time off work or school of 9% versus 25% with nasal saline (odds ratio 0.29, 95% CI 0.16 to 0.53).

Humidified air

Conflicting results leave considerable uncertainty about the impact of heated, humidified air on the common cold. Evidence for heated, humidified air comes from a systematic review and meta-analysis of six RCTs.[26] The trials were small, had a poor description of randomization and allocation concealment, and used a variety of measures that made pooling and comparisons difficult. Only two studies could be pooled for one outcome (the number of patients with persistent symptoms). The results were significantly different, with no overlap in confidence intervals (Peto odds ratio 0.10, 95% CI 0.04 to

0.27, in one study and 0.73, 95% CI 0.31 to 1.72 in the other study). As another example, one study found nasal resistance decreased with steam, whereas another found it increased.

Vitamin C

A systematic review of vitamin C for the treatment of colds found no effect on duration or severity of the common cold.[1] Evidence does not support the use of vitamin C in the treatment of the common cold.

Echinacea

A systematic review of echinacea for the treatment of colds found pooling was impossible because the RCTs were inconsistent with regards to formulations, definition of colds and outcomes measured.[3] The most common plant extract used was the aerial portion of the *E. purpurea* plant. In total severity and duration of colds, 1 of 6 studies reached significance in favour of echinacea. In sum cold scores at 2–4 days, 2 of 6 studies providing adequate data reached significance; at 5–10 days, 5 of 10 studies reached significance. Given the inconsistency in results, the benefits of echinacea for the treatment of the common cold are unclear.

Chinese medicinal herbs

A high-quality systematic review of Chinese medicinal herbs included 17 RCTs. Data could not be pooled because the same herbs were not used in any RCTs.[27] Only one trial showed significant improvement in the severity of symptoms. None of the six comparisons found significant overall improvement in colds. Although some studies found benefits in some outcomes (e.g., fewer patients with "no improvement"), other studies found controls were superior in other outcomes (e.g., "recovery"). Evidence does not support the use of Chinese medicinal herbs in the treatment of the common cold.

Ginseng

We could locate only one RCT for the acute treatment of the common cold with ginseng.[28] This pediatric trial did not report efficacy outcomes (symptoms or duration) but focused on adverse events, which were not increased with either standard- or low-dose ginseng. There is no evidence to support the use of ginseng in the treatment of the common cold.

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