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Soap versus sanitiser for preventing the transmission of acute respiratory infections in the community: a systematic review with meta-analysis and dose–response analysis

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ABSTRACT

Objective To compare the effectiveness of hand hygiene using alcohol-based hand sanitiser to soap and water for preventing the transmission of acute respiratory infections (ARIs) and to assess the relationship between the dose of hand hygiene and the number of ARI, influenza-like illness (ILI) or influenza events.

Design Systematic review and meta-analysis.

Data sources Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, Cumulative Index of Nursing and Allied Health Literature (CINAHL) and trial registries were searched in April 2020.

Inclusion criteria We included randomised controlled trials that compared a community-based hand hygiene intervention (soap and water, or sanitiser) with a control, or trials that compared sanitiser with soap and water, and measured outcomes of ARI, ILI or laboratory-confirmed influenza or related consequences.

Data extraction and analysis Two review authors independently screened the titles and abstracts for inclusion and extracted data.

Results Eighteen trials were included. When meta-analysed, three trials of soap and water versus control found a non-significant increase in ARI events (risk ratio (RR) 1.23, 95% CI 0.78 to 1.93); six trials of sanitiser versus control found a significant reduction in ARI events (RR 0.80, 95% CI 0.71 to 0.89). When hand hygiene dose was plotted against ARI relative risk, no clear dose–response relationship was observable. Four trials were head-to-head comparisons of sanitiser and soap and water but too heterogeneous to pool: two found a significantly greater reduction in the sanitiser group compared with the soap group and two found no significant difference between the intervention arms.

Conclusions Adequately performed hand hygiene, with either soap or sanitiser, reduces the risk of ARI virus transmission; however, direct and indirect evidence suggest sanitiser might be more effective in practice.

Strengths and limitations of this study

- ► Systematic review with meta-analysis and dose–response analysis of randomised controlled trials.
- ► Additional analysis of a subset of trials from a previously published systematic review and meta-analysis of physical interventions to reduce the spread of respiratory viruses.
- ► Conclusions are mostly from indirectness evidence, with direct evidence available from only four head-to-head trials.

INTRODUCTION

Acute respiratory infections (ARIs) cause a substantial annual health burden and much more so in the current COVID-19 pandemic. Globally, approximately 4 million deaths per year are caused by ARIs, with the current pandemic leading to just over 4.3 million deaths.[1 2] To minimise the potential threat of ARIs to public health, the implementation of effective preventive community-based measures is essential.[3 4]

Hand hygiene has previously been shown to be an effective intervention that reduces the transmission of the viruses and bacteria that cause ARIs.[5 6] It is a low-cost intervention that is applicable in all countries and all settings. Unlike vaccines that are disease specific, hand hygiene has the advantage of being applicable to multiple ARIs.[5] Despite the effectiveness and worldwide applicability of hand hygiene, important questions for policy and practice remain, such as the dose–response and relative effectiveness of different materials (alcohol-based hand sanitiser; soap and water). This systematic review aimed to address these questions. This review is an additional analysis of a subset of randomised trials that were included in a large systematic review that addressed all physical interventions (eg, face masks, personal protection, hand hygiene and quarantining) to prevent the transmission of ARIs.[5]

METHODS

We aimed to find, appraise and synthesise studies of the effectiveness of hand hygiene interventions in the community for preventing ARI transmission. For this systematic review, a subset of articles relating to hand hygiene interventions were identified from a recently updated and published systematic review of all physical interventions for preventing ARI transmission. This review was not registered on PROSPERO as this review is an additional analysis of a subset of trials from a published Cochrane systematic review.[5]

Inclusion criteria and study source

Participants

We included studies of participants of any age, gender or condition. Trials in healthcare settings were excluded.

Interventions

We included studies of interventions that compared a hand hygiene intervention (ie, hand washing with soap and water or hand sanitiser) with a control intervention, or which compared two hand hygiene interventions.

Outcomes

We only included studies that reported a measure of ARI, such as influenza-like illness (ILI), influenza or respiratory infections, and this was our primary outcome. Studies were also eligible if they reported on ARI consequences (eg, days off work, complications, hospitalisation or death, if clearly reported as consequences of the respiratory illness), and these were our secondary outcomes.

Study design

Randomised controlled trials (RCTs) and cluster randomised controlled trials (C-RCTs) were eligible.

Search strategy

RCTs and C-RCTs studying the effectiveness of hand hygiene interventions in the transmission of ARIs were identified from the parent 2020 systematic review.[5] Studies for that review were identified via a search of the Cochrane Central Register of Controlled Trials, Embase and Cumulative Index of Nursing and Allied Health Literature (CINAHL), covering the dates October 2010 to 9 March 2020. The search string (see online supplemental file 1) was designed for PubMed using the word frequency analyser and then translated for use in other databases using the Polyglot Search Translator.[7] A backwards and forward citation analysis, using Scopus, was conducted on all new studies retrieved. Search and citation analysis results were screened using the RobotSearch tool to remove all obvious non-RCTs.[8] While the analysis of the parent review was being conducted, a new Cochrane review of rinse-free handwashing in school and preschool children was published, and we also screened its included studies for possible eligible studies.[9] Three authors (TH, MB and NK) independently reviewed the titles and abstracts of identified studies to assess eligibility for inclusion. Discrepancies were resolved by consensus.

Screening and data extraction

Two review authors (MB and NK) independently screened the titles and abstracts for inclusion against the inclusion criteria. One author retrieved the full text and two authors screened the full-texts for inclusion. Any disagreements were resolved by discussion between the authors or with a third author. Data were independently extracted by two authors (MB and NK) on: volume or weight of material (eg, sanitiser or soap) used per person per day and number of handwashes per person per day. When not reported directly, we estimated usage where possible (see table 1). For estimation purposes, we used data on the average amount of material used per person per handwash as reported; if data were not reported, we assumed 0.035 g of soap or 1.5mL of liquid used per handwash.[10] A data extraction form for outcome data was piloted on two studies in the review. The following data were extracted from the parent systematic review[5]: (1) study characteristics; (2) risk of bias assessments; (3) type of handwashing intervention(s) (eg, soap, sanitiser and gel); and (4) RRs, log RR and SE values for ARI or ILI or influenza (including the outcome with most events from each study).

Risk of bias assessment

Risk of bias was assessed with the Cochrane Collaboration's Risk of Bias tool 1.[11] Author pairs from the parent review independently screened for: the method of random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), outcome reporting (attrition bias) and selective reporting (reporting bias). Disagreements were resolved by discussion or a third assessor. For each item, risk was either 'high', 'low' or 'unclear'.

Data analysis

To assess the relationship between handwashes per person per day and the number of ARI or ILI or influenza events, we conducted the following analyses: (1) only studies whose number of handwashes could be estimated (regardless of the type of handwash material), subgrouped by the type of handwash material (soap vs sanitiser vs combination of sanitiser and soap) and (2) all studies (whether or not the number of handwashes could be estimated), subgrouped by the type of handwash material (soap vs sanitiser vs combination of sanitiser and soap). We used a χ^2 test to test for subgroup interactions. Meta-analyses were conducted using *Review Manager 5.4*.

We used RRs for results, reporting the number of participants with an event. We undertook meta-analyses where data were sufficient to pool (when ≥2 studies or comparisons reported the same outcome). A random effects model was used because we expected some heterogeneity in the populations, interventions and outcomes of the included studies. The individual was used as the unit of analysis, where possible. However, where data on the number of individuals with primary and secondary outcomes of interest were not available, we extracted and used data for the closest equivalent ratio, for example, a rate ratio based on the ratio of total

Table 1 Characteristics of included studies

First author (country, year)	Study design	Setting	Study period in months	Population (age range)	Number of participants	Type of hand hygiene intervention*					Duration of intervention	Number of handwashes/ day	Type of infection	Calculations used for the number of handwashes/day (if applicable)	Amount of soap or alcohol used (mL or g)/ person/day	Calculations used for the amount of alcohol or soap in mL or g/person/day (if applicable)
						Staff training/ education	Classroom activities	Sanitiser	Soap	Combined (sanitiser and soap)						
Azor-Martinez[12] (Spain, 2018)	C-RCT	CCCs	7	Ch (0–3 years)	911 Ch; 24 CCC	✓	✓	✓	✓		8 months	7 (sanitiser)	ARI	Each child used sanitiser between 6 and 8 times/day	10.5 mL	Assume mean 7 uses per day, 1.5 mL mean per use
Biswas[16] (Bangladesh, 2019)	C-RCT	Sch	4	Ch (5–10 years)	10 855 Ch	✓	✓	✓			10 weeks	2.87	Influenza	We calculated the percentage of handwashing practices by dividing the number of handwashing instances by the total number of handwashing opportunities. There were 921 handwashing opportunities in intervention group (page 5). 604 (66%) schoolchildren in the intervention group washed their hands (at end line) and 5077 students in the intervention group. 4.3 mL/person/day and assumed 1.5 mL of sanitiser use per wash gives 2.87 washes/day	4.3 mL	N/A
Correa[17] (Colombia, 2012)	C-RCT	CCC	8	Ch (0–5 years)	42 CCC	✓		✓			8 months	5.261	ARI and GI	We assumed that one alcohol-based hand sanitiser push=1 instance of hand wash and took into account the proportion of community and preschools, as in the calculation for mL/person/ day, gives 5.261 pushes (or handwashes) per day	3.16 mL	32 community centres and 10 preschools included the trial, distributed among the intervention and control arms; assumed the 32 versus 10 ratio to estimate the increase in the number of pushes: 10/42 * 4.5 for preschools+32/42*5.5 for community centres=5.261 average number of pushes overall. 5.261 pushes at 1000 mL/1666 pushes=3.16 mL
Cowling[19] (Hong Kong, 2008)	C-RCT	HH	7	A and Ch (NR)	198 HH	✓				✓	9 days	NR	Influenza		NR	
Cowling[18] (Hong Kong, 2009)	C-RCT	HH	8	A and Ch (NR)	407 HH	✓				✓	1 week	NR	Influenza		NR	
Hubner[20] (Germany, 2010)	RCT	O	12	A (NR)	1230 A	✓		✓			1 year	3.84	ARI and GI	0.19 * 6 (assumed >5 handwashes means 6); 0.598 * 4 (average of 3–5); 0.205 * 1.5 (average of 1–2)+0.007 * 0 to get the mean number of handwashes per day across the whole group=3.84	11.52 mL	0.19 * 6 (assume >5 handwashes means 6); 0.598 * 4 (average of 3–5); 0.205 * 1.5 (average of 1–2)+0.007 * 0 to get the mean number of handwashes per day across the whole group=3.84 mean handwashes/person * 3 mL per handwash=11.52
Larson[21] (USA, 2010)	C-RCT	HH	20	A and Ch (NR)	509 HH	✓		✓			19 months	1.77	ILI and influenza	44.2% in the education group (not handwash group) reported using hand sanitiser 'occasionally at some point during the study' and 56.9% of these reported using hand sanitiser 1–2× in previous 24 hours'. 2.65 mL/person/day at 1.5 mL sanitiser per handwash=1.77 handwashes/day	2.65 mL	4.5 people/household; 30 days /month; 358 mL handwash per month gives: 2.65 mL/ person/day

Continued

Table 1 Continued

First author (country, year)	Study design	Setting	Study period in months	Population (age range)	Number of participants	Type of hand hygiene intervention*					Duration of intervention	Number of handwashes/ day	Type of infection	Calculations used for the number of handwashes/day (if applicable)	Amount of soap or alcohol used (mL or g)/ person/day	Calculations used for the amount of alcohol or soap in mL or g/person/day (if applicable)
						Staff training/ education	Classroom activities	Sanitiser	Soap	Combined (sanitiser and soap)						
Lennell[13] (Sweden, 2008)†, ‡	C-RCT	CCC	7	Ch (mean age 3 years)	1517 Ch; 29 CCC	✓		✓	✓		30 weeks	4 (sanitiser)	NC	N/A	6 mL	N/A
Little[22] (England, 2015)	RCT	Onl	26	A (≥18)	20 066 A	✓				✓	4 months	7.48	ARI	0.04 * 1 avg+0.10 * 3.5 avg+0.22 * 5.5 avg+0.26 * 8 avg+0.38 * 10 (assuming >=10 at 10)=7.48 avg	NR	
Nicholson[23] (India, 2014)	C-RCT	HH	10	Ch (5–18 years)	NR	✓	✓		✓		41 weeks	16	ARI and GI	The median soap consumption was found to be 45 g per household per week in control households compared with 235 g in intervention households. 5.6 g/ person/day at 0.35 g of soap per wash=16 handwashes a day	5.60 g	235 g/week; six people/ household; gives: 5.595/ person/day
Pickering[14] (Kenya, 2013)	C-RCT	Sch	§	Ch (2–13 years)	6 Sch	✓	✓	✓	✓		8 weeks	NR	ARI and GI		NR	
Ram[24] (Bangladesh, 2015)	RCT	HH	18	A (NR)	NR	✓			✓		10 days	5.89	ILI and influenza	2.06 g soap/person/day at 0.35 g of soap per wash=5.89 washes/ day	2.06 g	Figure 3 in Ram *et al*[24] reports median/capita soap use in grams by day of enrolment, days 2–12. Median/capita soap use in grams on last day (day 12) was 2.06 g
Roberts[25] (Australia, 2000)	C-RCT	CCC	8	Ch (0–3 years)	23 CCC	✓	✓	✓			8 months	NR	ARI		NR	
Sandora[26] (USA, 2005)	C-RCT	HH	5	A (NR) and Ch (6 months to 5 years)	292 families			✓			5 months	5.2	ARI and GI	N/A	5.2 mL	Assumed 1 mL/hand sanitiser use (may not be correct as it is one pump but could have done >1 pump of sanitiser each handwash), 5.2 uses/ day/person
Savolainen-Kopra[15] (Finland, 2012)§,‡	C-RCT	O	18	A	683 A; 21 office work units; six corporations	✓		✓	✓		15–16 months	6.1 (soap) and 6.9 (sanitiser)	ARI and GI	N/A	NR	
Simmerman[27] (Thailand, 2011)	C-RCT	HH	16	A and Ch (NR)	442 Ch; 1147 household members	✓			✓		3 weeks	4.7	Influenza	N/A	7.71 mL	54 mL/person/week=7.714 mL/ person/day
Stebbins[28] (USA, 2011)	C-RCT	Sch	14	Ch (NR)	3360 Ch; 10 Sch	✓		✓			1 influenza season	2.4	Influenza	N/A	1.44 mL	0.6 mL per use*2.4 times per day=1.44
Zomer[29] (Netherlands, 2015)	C-RCT	CCC	7	Ch (6 months to 3.5 years)	545 Ch; 71 CCC	✓				✓	6 months	NR	ARI and GI		NR	

*Only hand hygiene arms of the included studies.
†This study was not included in the dose–response analysis as the infection was reported for any infection (not specific to respiratory infections).
‡Studies not included in the meta-analysis.
§Bathrooms at the workplaces were equipped with liquid hand soap (all arms).
A, adults; ARI, acute respiratory infections; avg, average; CCC, childcare centres; Ch, children; C-RCT, cluster randomised controlled trial; GI, gastrointestinal infections; HH, households; ILI, influenza-like illness; N/A, not applicable; NC, not clear; NR, not reported; O, offices; Onl, online; RCT, randomised controlled trial; Sch, schools.

number of events (eg, ARI events) in each group irrespective of the number per person. We contacted investigators to provide missing data where feasible. We used the I^2 statistic to measure heterogeneity among the included trials. We referred to the Cochrane Handbook in the interpretation of the I^2 statistic and were guided by the following ranges: 0%–40%: may represent non-significant heterogeneity; 30%–60%: may represent moderate heterogeneity; 50%–90%: may represent substantial heterogeneity; 75%–100%: considerable heterogeneity.[11] Data were sufficient to conduct a subgroup analysis by comparison (soap vs sanitiser vs combination soap and sanitiser). To ensure we accounted for the clustering effect in the cluster RCTs, we extracted the appropriate cluster-adjusted estimates from the trial reports and used the generic inverse variance method of meta-analysis.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart (figure 1) shows the number of trials identified from the 2020 parent systematic review[5] and other sources. Eighteen trials were assessed as eligible;

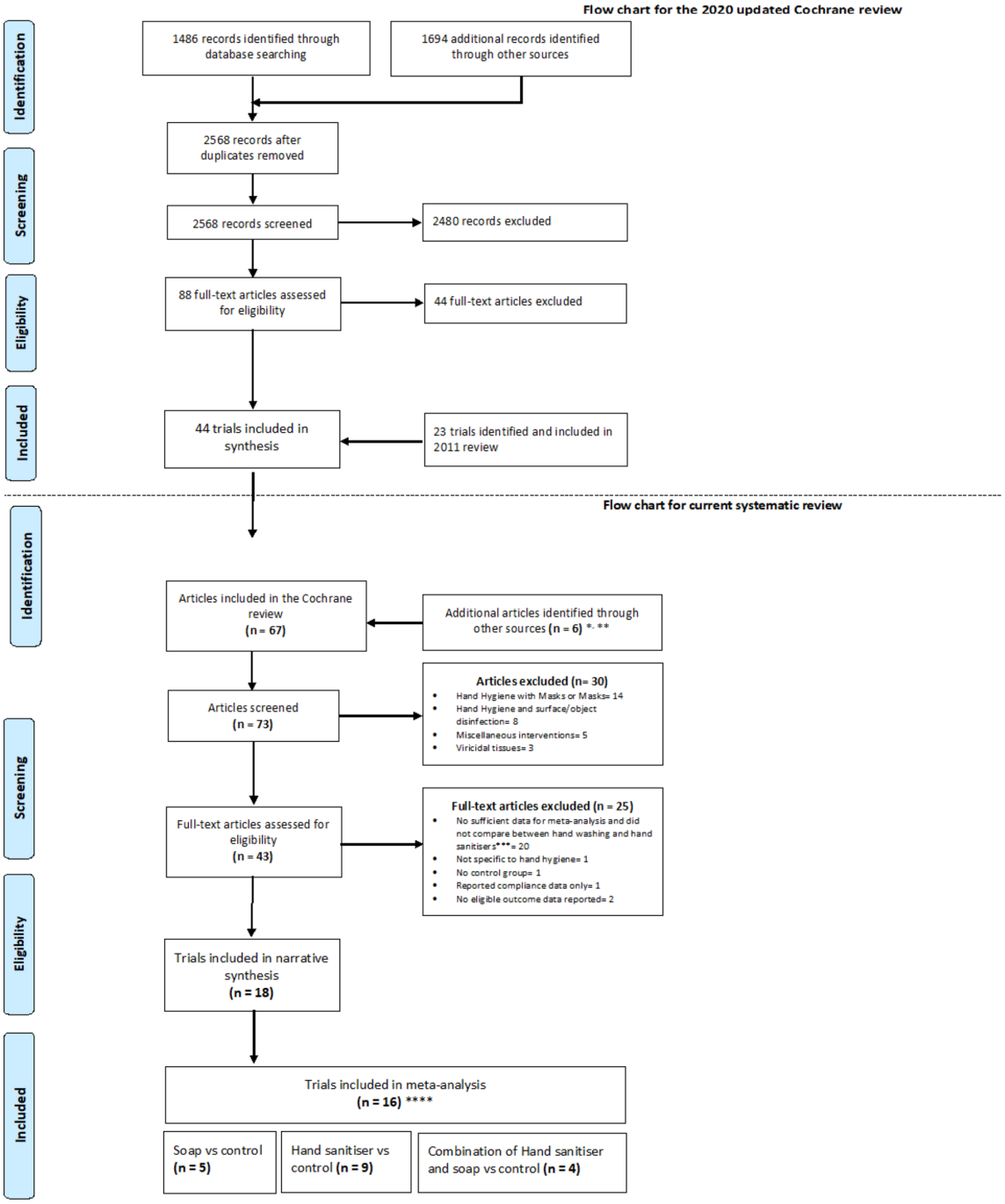


Figure 1 PRISMA flow chart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

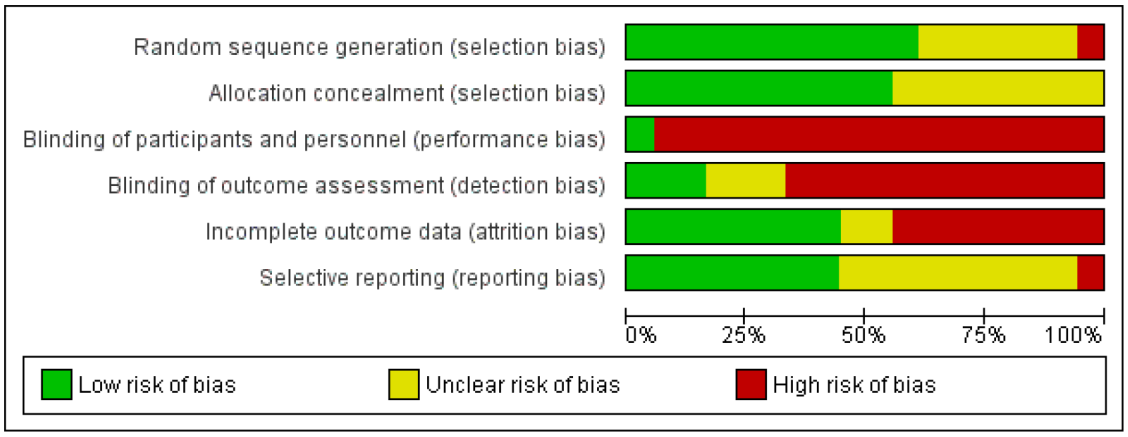


Figure 2 Overall risk of bias – presented as percentages across all included RCTs. RCTs, randomised controlled trials.

four were head-to-head comparisons of hand sanitiser and soap and water[12–15] and 16 compared hand hygiene with a control.[12 14 16–29] Table 1 presents study and intervention characteristics. Online supplemental file 2 contains a summary of the comparator conditions. The majority of trials used existing handwashing practices as the comparator condition. One trial additionally provided education on hand hygiene, and four provided health promotion education and provided participants with education on the prevention and treatment of respiratory tract infections. None of the studies provided control group participants with any hand hygiene materials.

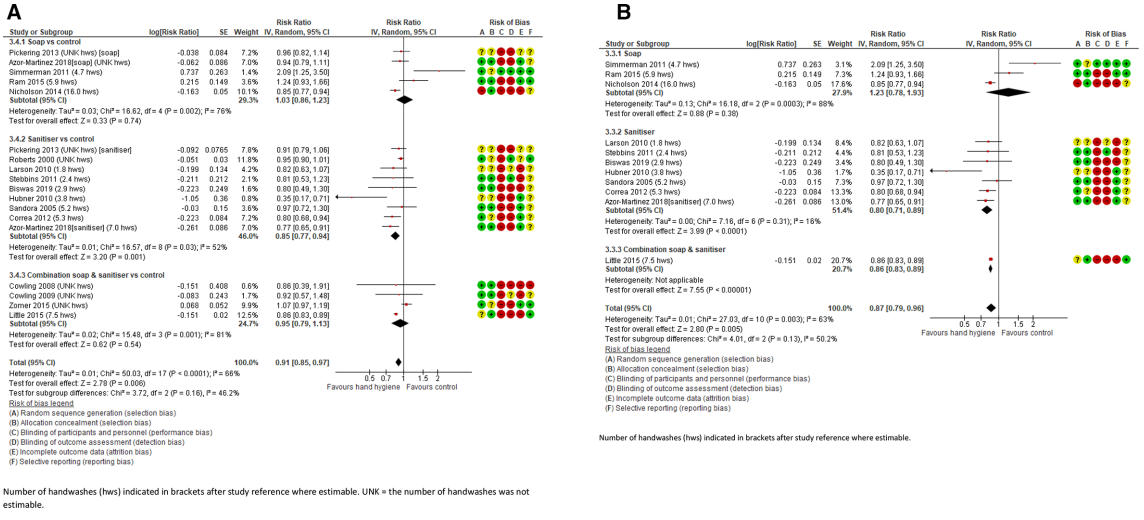
Risk of bias assessment

Most studies (95%) were unblinded due to the nature of the intervention, leading to a high risk of bias judgement (figure 2). See online supplemental file 3 for risk of bias assessment for each individual trial. Only one study was blinded to staff.[27] Blinding of outcome assessment and attrition bias was poor across 67% and 44% of studies, respectively. Sequence generation and allocation concealment had a low risk of bias assessment in about half of the studies. Fifty per cent of studies had unclear risk of bias for selective outcome reporting due to the lack of sufficient information.

Trials of hand sanitiser or soap and water versus control

Figure 3A presents the meta-analysis of all trials, regardless of whether the number of handwashes could be estimated. Combining the five trials of soap and water hand hygiene versus control found a non-significant increase in ARI events: RR: 1.03 (95% CI 0.86 to 1.23) but with high heterogeneity. The nine trials of hand sanitiser versus control found a significant reduction in ARI events: RR: 0.85 (95% CI 0.77 to 0.94), providing some indirect evidence in favour of hand sanitiser.

A similar pattern of results was found when only trials for which the number of handwashes could be estimated were considered (figure 3B), combining the three trials of soap and water hand hygiene versus control found a non-significant increase in ARI events: RR: 1.23 (95% CI



Number of handwashes (hws) indicated in brackets after study reference where estimable. UNK = the number of handwashes was not estimable.

Figure 3 (A) Meta-analysis of all studies (regardless of whether the number of handwashes could be estimated) regardless of the type of handwash material (soap vs sanitiser vs combination of sanitiser and soap). (B) Meta-analysis of studies whose number of handwashes could be estimated, subgrouped by the type of handwash material (soap vs sanitiser vs combination of sanitiser and soap).

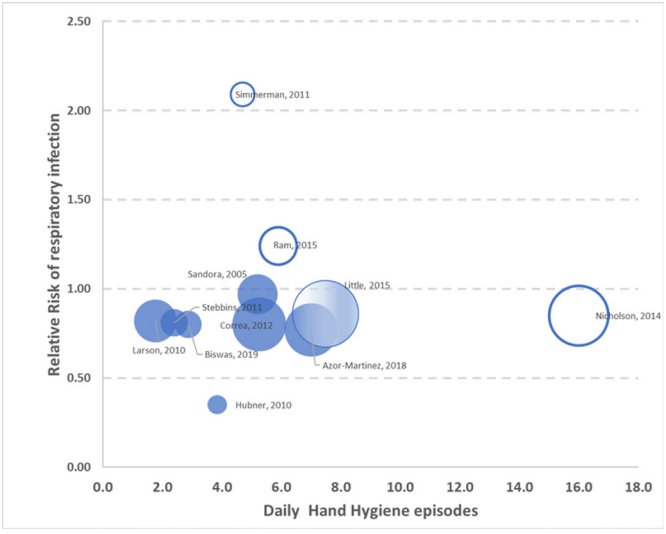


Figure 4 Hand hygiene frequency ('dose') versus risk of respiratory infection (ARI, ILI or influenza). ARI, acute respiratory infection; ILI, influenza-like illness.

0.78 to 1.93) but with high heterogeneity (figure 3B). Combining the seven trials of hand sanitiser versus control found a significant reduction in ARI events: RR: 0.80 (95% CI 0.71 to 0.89).

Dose–response relationship: hand hygiene frequency versus risk of respiratory infection (ARI, ILI or influenza)

Eleven of the trials provided sufficient information to estimate the dose of hand hygiene, which we converted to number of hand hygiene events per day. Plotted against the relative risk of ARIs, there is little dose–response relationship evident for hand sanitiser (figure 4). The difference in effectiveness between hand sanitiser and soap and water does not appear to be explained by a difference in frequency. The cluster randomised trial by Little and colleagues[22] primarily used soap and water but also offered participants free hand sanitiser; only 18% reported collecting the sanitiser.

Head-to-head trials of hand hygiene with hand sanitiser versus with soap and water

Four trials directly compared hand sanitiser with soap and water: two in childcare centres, one at a primary school and one in workplaces. In a cluster randomised trial of children and staff in Swedish childcare centres, those at centres who were randomised to use an alcohol-based oily disinfectant gel (70% ethanol) after regular hand washing had a reduction in absenteeism rate of 12% (95% CI 4% to 20%) compared with control centres which used only soap and water.[13] The three-arm cluster randomised trial of 24 childcare centres in Spain: educational and hand hygiene measures (one with soap and water; another with hand sanitiser) and a control group found children in the sanitiser group had a 13% lower (95% CI 6% to 28%) risk of respiratory infection than children in the soap and water group.[12]

In Kenya, a cluster randomised trial assigned two primary schools to receive a handwashing with soap and water intervention, two to receive a sanitiser intervention and two were a control.[14] Compared with control group students, both intervention groups had a reduction in observed rhinorrhoea (RR 0.77, 95% CI 0.62 to 0.95 for both sanitiser vs control and soap vs control). No significant differences between the sanitiser and soap groups were observed for respiratory outcomes. The three-arm trial in six companies in Finland randomised workplaces to equip workplace bathrooms with liquid hand soap (soap and control arms) or alcohol-based hand rub.[15] Participants in the intervention arms also received guidance on additional strategies for limiting infection transmission. Before the onset of the 2009 influenza pandemic (and the subsequent national hand hygiene campaign), a statistically significant (p=0.002) difference in the infection episodes was observed between the control (6.0 per year) and the soap-and-water arm (5.0 per year) but not between the control and the alcohol rub arm (5.6 per year). Neither intervention had an effect on work absenteeism.

DISCUSSION

Based on both indirect and direct (head to head) trials, hand hygiene using alcohol-based hand sanitiser appears more effective at reducing ARI transmission than hand hygiene using soap and water, with the difference in effect not explained by the difference in frequency of hand hygiene. This is an important finding, as most guidelines consider the two hand hygiene processes as equivalent, based on microbiological data for correctly performed processes.

The apparent greater effectiveness of hand sanitiser may be explained by its greater convenience, the lesser time required to perform hand hygiene, more sustained compliance with hand hygiene and less irritation to the skin.[30] From our review of current research, we cannot determine the relative contribution of these behavioural elements, and hence further research is warranted to examine those contributions and ways to improve each.

Limitations of this review are that conclusions are mostly from indirectness evidence, with direct evidence available from only four head-to-head trials and that it was not possible to estimate the dose of hand hygiene for some trials. The variable duration of the interventions (which ranged from 2 to 26 months) in the included studies may have impacted the reported intervention adherence and hence the comparability of it.

A recent Cochrane review of the effect of rinse-free handwashing, compared with traditional hand hygiene, on absenteeism for ARI in preschool and school children reported a significant reduction in absenteeism of 9 days per 1000 available days for children in the rinse-free group, with the results coming from six randomised trials.[9] The effectiveness of handwashing with materials other than sanitiser or soap and water, such as ash, which may be used in low-income countries, has mostly been examined in observational studies with uncertain effects.[31]

Although the current evidence modestly favours hand sanitiser, further trials of hand hygiene methods are warranted. Any such trials should include a set of process measures looking at the 'intervention fidelity' elements, such as frequency and correctness of hand hygiene processes. Meanwhile, policy documents and public guidance should continue to suggest both but indicate that current evidence somewhat favours sanitiser for behavioural rather than biological reasons and that it should be recommended where feasible.

CONCLUSIONS

Hand hygiene has a modest but important role in reducing the transmission of ARIs. Adequately performed hand hygiene, with either soap or sanitiser, reduces the risk of acute respiratory virus transmission. However, from both the direct and indirect comparisons in this review, sanitiser appears more effective in practice. While further head-to-head randomised trials are warranted, the current evidence appears sufficient to promote the use of hand sanitiser as the primary means for many everyday situations.

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