Effectiveness of handwashing with soap for preventing acute respiratory infections in low-income and middle-income countries: a systematic review and meta-analysis

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Summary

Background **Acute respiratory infection (ARI) is a leading cause of morbidity and mortality globally, with 83% of ARI mortality occurring in low-income and middle-income countries (LMICs) before the COVID-19 pandemic. We aimed to estimate the effect of interventions promoting handwashing with soap on ARI in LMICs.**

Methods **In our systematic review and meta-analysis, we searched MEDLINE, Embase, Web of Science, Scopus, Cochrane Library, Global Health, and Global Index Medicus for studies of handwashing with soap interventions in LMICs from inception to May 25, 2021. We included randomised and non-randomised controlled studies of interventions conducted in domestic, school, or childcare settings. Interventions promoting hand hygiene methods other than handwashing with soap were excluded, as were interventions in health-care facilities or the workplace. The primary outcome was ARI morbidity arising from any pathogen for participants of any age. Secondary outcomes were lower respiratory infection, upper respiratory infection, influenza confirmed by diagnostic test, COVID-19 confirmed by diagnostic test, and all-cause mortality. We extracted relative risks (RRs), using random-effects meta-analysis to analyse study results, and metaregression to evaluate heterogeneity. We assessed risk of bias in individual studies using an adapted Newcastle-Ottawa scale, and assessed the overall body of evidence using a Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. The study is registered with PROSPERO, CRD42021231414.**

Findings **26 studies with 161 659 participants met inclusion criteria, providing 27 comparisons (21 randomised). Interventions promoting handwashing with soap reduced any ARI compared with no handwashing intervention (RR 0·83 [95% CI 0·76–0·90], I^2 88%; 27 comparisons). Interventions also reduced lower respiratory infections (0·78 [0·64–0·94], I^2 64%; 12 comparisons) and upper respiratory infections (0·74 [0·59–0·93], I^2 91%; seven comparisons), but not test-confirmed influenza (0·94 [0·42–2·11], I^2 90%; three comparisons), test-confirmed COVID-19 (no comparisons), or all-cause mortality (prevalence ratio 0·95 [95% CI 0·71–1·27]; one comparison). For ARI, no heterogeneity covariates were significant at p<0·1 and the GRADE rating was moderate certainty evidence.**

Interpretation **Interventions promoting handwashing with soap can reduce ARI in LMICs, and could help to prevent the large burden of respiratory disease.**

Funding **Bill & Melinda Gates Foundation, Reckitt Global Hygiene Institute, and UK FCDO.**

Published Online
April 27, 2023
https://doi.org/10.1016/S0140-6736(23)00021-1

See Online/Comment
https://doi.org/10.1016/S0140-6736(23)00266-0

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Introduction

By the end of 2021, the ongoing COVID-19 pandemic had caused an estimated 18 million excess deaths.[1] SARS-CoV-2 is a particularly dangerous cause of epidemic acute respiratory infection (ARI), but every year there is a large endemic respiratory disease burden—4% of global disability-adjusted life-years (DALYs) and 2·5 million deaths in 2019 were attributable to ARIs.[2] Very young and very old people are at particularly high risk,[3] with an estimated 740 000 deaths of children younger than 5 years attributable to ARIs in 2019.[4] Before the COVID-19 pandemic, 83% of the ARI mortality burden was in low-income and middle-income countries (LMICs) and nine of ten lower respiratory episodes occurred in LMICs.[3]

ARIs can be disaggregated into lower respiratory infections and upper respiratory infections, depending on whether the infection's primary location is below the larynx (lower respiratory infection) or above it (upper respiratory infection). Lower respiratory infections are responsible for 3·8% of total DALYs and upper respiratory infections are responsible for 0·3%, meaning that lower respiratory infections comprise 93·9% of ARI DALYs.[2] Lower respiratory infections such as pneumonia and bronchiolitis affect the lungs, with symptoms including difficulty breathing and rapid respiratory rate. Upper respiratory infections such as the common cold affect the sinuses and throat, with symptoms including a runny nose (coryza) and a sore throat (pharyngitis). A cough can be a symptom of lower or upper respiratory infections.[5] Upper respiratory infections are predominantly viral, whereas lower respiratory infections can be bacterial or viral.[6]

Research in context

Evidence before this study

Previous systematic reviews have consistently found that interventions promoting handwashing with soap reduce acute respiratory infection (ARI). However, the most recent meta-analysis is for viral ARI only, and included only five studies in low-income and middle-income countries (LMICs), where ARI burden is largest. The last meta-analysis for any ARI was reported in 2008, including only one LMIC study. No previous meta-analysis has distinguished between lower and upper respiratory infections. We searched MEDLINE, Embase, Web of Science, Scopus, Cochrane Library, Global Health, and Global Index Medicus for handwashing with soap intervention studies in LMICs from inception to May 25, 2021. We included randomised and non-randomised controlled studies of interventions conducted in domestic, school, or childcare settings. The primary outcome was ARI morbidity arising from any pathogen.

Added value of this study

This analysis provides updated estimates of the effectiveness of handwashing with soap in LMICs on each of ARI, lower respiratory infection, upper respiratory infection, and influenza confirmed by diagnostic test. In random effects meta-analysis of 27 comparisons, interventions promoting handwashing with soap reduced ARI by about 17% (relative risk 0·83 [95% CI 0·76–0·90], I^2 88%) compared with no handwashing intervention. These estimates are important for up-to-date assessments of the attributable burden of disease. We provide separate estimates for lower and upper respiratory infections, which has not previously been done. We also draw on evidence excluded from earlier reviews by including non-randomised intervention studies. Meta-regression and sensitivity analysis show that the main finding is unaltered as a result.

Implications of all the available evidence

Interventions promoting handwashing with soap can reduce ARI. Such interventions are an important means of preventing ARIs in LMICs. In comparison with the attention given to handwashing during epidemics of respiratory disease, handwashing campaigns in normal times are rare. The scarcity of such campaigns might be a missed opportunity, and promoting handwashing with soap more broadly could reduce the large endemic burden of respiratory disease.

ARI-causing pathogens can be transmitted via airborne, surface, or person-to-person contact routes.[7] Handwashing with soap can prevent many ARIs by mechanically removing pathogens from hands, and by rupturing many bacteria and viruses. There is no biological reason to assume handwashing with soap interrupts transmission of upper and lower respiratory infections differently. Recent estimates of annual ARI deaths attributable to inadequate hand hygiene range from 270 000 to 370 000,[8,9] in addition to 165 000 attributable deaths from diarrhoeal disease.[9] Handwashing practices at key moments are less prevalent in LMICs compared with high-income countries (HICs)[10] for many reasons, including reduced access to water supply on premises or to handwashing facilities with soap and water.[11]

Four limitations of the existing systematic review evidence for the effect of handwashing with soap on ARIs motivated our review because they limit understanding of the likely effect size and quantification of the attributable burden of disease. First, the evidence base is out of date. Although there have been meta-analyses focusing on viral illness or influenza only,[12,13] the latest published meta-analysis to include any ARI as an outcome was reported in 2008 by Aiello and colleagues,[14] who estimated that hand hygiene improvements reduced ARIs by 21% (95% CI 5–34). Second, the evidence base is misaligned with the geography of the endemic disease burden. The meta-analysis by Aiello and colleagues included only one LMIC study,[15] and the most recent study (focused on viral illness) included only five.[12] Although another systematic review conducted in 2017 by McGuinness and colleagues did focus on ARI in LMICs and included 14 studies, the authors did not conduct a meta-analysis.[16] Third, reviews have been restrictive in terms of included study designs. The review by McGuinness and colleagues included only randomised controlled trials,[16] whereas a recent systematic review of the effect of handwashing on diarrhoeal disease included ten non-randomised studies.[17] Fourth, meta-analyses have not distinguished between lower and upper respiratory infections, as applied in global burden of disease estimation.[2]

In this Article, we aimed to assess the effect of interventions to improve handwashing with soap in domestic, school, and childcare settings on ARIs in LMICs.

Methods

Study design

Our systematic review and meta-analysis is reported according to PRISMA 2020 guidelines.[18] Many aspects of the methods are aligned with a recent systematic review on the effectiveness of handwashing with soap on diarrhoea by Wolf and colleagues,[19] such as included types of study design, risk of bias scoring, and Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).

Search strategy and selection criteria

We searched MEDLINE, Embase, Web of Science, SCOPUS, the Cochrane Library, Global Health, and Global Index Medicus for literature published in English or French from inception to May 25, 2021. Our search strategy (appendix pp 3–4) combines terms for ARIs with terms for hand hygiene promotion or provision refined from recent reviews.[16,17] We also screened the reference lists of included full texts and previous relevant systematic reviews. We used Mendeley (Elsevier 2020, Amsterdam, Netherlands) for de-duplication, Rayyan for managing blinded title and abstract screening,[20] and Microsoft Excel for data extraction. Two reviewers (IR and SB) independently screened titles, abstracts, and full texts of studies identified during searches. Differences between reviewers over title and abstract screening, full text review, and reasons for exclusion were reconciled with a third reviewer (OC).

Populations eligible for this review were anyone residing in LMICs (World Bank 2019–20 classification).[21] Eligible settings included domestic (households), schools (educational institutions, typically for children aged 5–15 years), or childcare (typically daycare for children aged 2–4 years). Eligible interventions were those promoting the practice of handwashing with soap, including providing associated facilities and products. Examples of promotion activities include mass media campaigns and door-to-door visits, and examples of facilities and products include handwashing stations and soap. Eligible interventions could be delivered at any level (eg, individual, household, and community). We excluded interventions exclusively promoting anything other than handwashing with soap, such as alcohol-based handrubs or anti-microbial towels. We included studies of combined interventions if they reported effect estimates separately for the handwashing component or if handwashing was clearly a major component (appendix p 2). We excluded interventions in health-care facilities or the workplace (including non-domestic animal husbandry).

We included study designs with interventions tested against a control group that did not receive the respective interventions or that received a different intervention or placebo. Eligible study designs included: individual and cluster-randomised controlled trials; and quasi-randomised and non-randomised controlled trials (eg, those with controlled before-and-after and interrupted time-series designs). Studies without interventions (eg, assessing self-reported handwashing as a risk factor) were excluded. We included studies that reported relative risk (RR) estimates and CI, or the data required to calculate them. When CIs could not be calculated we contacted the authors and, if still not feasibly calculated, we included the study in the review but did not include it in meta-analysis.

The primary outcome was all-cause ARI morbidity assessed through self-report, caregiver report, or clinical confirmation. In line with previous reviews,[16,22] our definition of ARI includes events classified as lower respiratory infection, upper respiratory infection, or infection in an unclassified location (eg, when location was not specified, or when the case definition included symptoms of both upper and lower respiratory infections). We pre-specified five secondary outcomes: lower respiratory infection morbidity, upper respiratory infection morbidity, influenza confirmed by diagnostic test, COVID-19 confirmed by diagnostic test, and all-cause mortality.

See Online for appendix

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Data analysis

We extracted effect size estimates and CIs, study setting, length of follow-up, characteristics of interventions, and whether studies reported results disaggregated by sex. We extracted effects on ARIs for all age groups reported. Data extraction and risk of bias assessment were performed independently by two reviewers (IR and SB) using a structured Excel spreadsheet. Differences between reviewers were reconciled by discussion, with recourse to a third reviewer (OC) if necessary. We contacted study authors when required data were not reported.

We extracted RRs from intention-to-treat analysis in the following order of preference: prevalence ratio or risk ratio, rate ratio, and then odds ratio. When RRs and CIs were not presented,[23,24] we calculated them from available data using standard formulas.[25] We converted odds ratios to risk ratios when control group risk was reported. We included risk ratios, prevalence ratios, and rate ratios without conversion. For non-randomised studies, we extracted adjusted effect size. For randomised studies reporting only effect size without adjustment, we extracted that effect size. However, for randomised studies that reported both adjusted and unadjusted effect size, we extracted adjusted effect size. For randomised studies reporting multiple adjusted effect sizes,[26] we extracted that which was reported as the primary result.

In cases of multiple comparisons within a single study (eg, multiple timepoints, age groups, or intervention groups), effect sizes were combined using methods described by Borenstein and colleagues.[27] Different effect sizes from different participants (eg, age groups) were combined as independent subgroups.[28] Different effect sizes from the same participants (eg, timepoints) were combined, accounting for correlation.[26] When multiple intervention groups met the inclusion criteria but were compared with a single control group, we combined effect sizes if handwashing promotion components of interventions were sufficiently similar.[15,24,29,30] However, when effect sizes were provided for a handwashing only group and for handwashing alongside other interventions, we used effect sizes from the handwashing only group.[31,32] When studies reported multiple recall periods for the same outcome (eg, 2-day and 7-day recall), we used the shortest period.[33]

We extracted effect sizes for all ARI-related outcomes of relevance to our primary and secondary outcomes. When studies reported multiple ARI symptoms and case definitions, we used an order of preference for deciding which to include in our primary outcome of any ARI. The hierarchy includes both lower and upper respiratory infection symptoms—eg, a cough can be a symptom of both. The order, including numbers of studies (of n=26) contributing, was: cough or difficulty breathing (CoDB; n=8); variants on CoDB (n=7); influenza-like illness (n=3); multiple lower respiratory infection or upper respiratory infection symptoms (n=6); absence from school due to ARI (n=2); and test-confirmed infection (n=0). The appendix (p 7) includes a table of the exact outcomes included in our “any ARI” analysis. The appendix (p 5) also includes the rationale for the hierarchy—comparability. First, the outcome selected should be whichever is most similar to the outcome measured in the majority of studies, which was CoDB and its variants (n=15). Second, outcomes should be collected in as similar a way as possible. Since almost all studies (n=23) measured caregiver-reported or self-reported outcomes only, for our primary outcome we chose caregiver-reported outcomes over test-confirmed outcomes (these were analysed separately as a secondary outcome). For the lower respiratory infection analysis, we included outcomes with lower respiratory infection-specific symptoms (eg, difficulty breathing), preferentially selecting outcomes based on watch-timed respiratory rate if available (appendix p 6). For the upper respiratory infection analysis, we included outcomes with upper respiratory infection-specific symptoms (eg, congestion and runny nose).

We assessed risk of bias in individual studies using an adapted Newcastle-Ottawa scale applied in previous systematic reviews of the effect of handwashing with soap on diarrhoea.[17,19] The scale considers seven areas of bias: selection bias, response bias, follow-up bias, misclassification bias, bias in outcome assessment, bias in outcome measurement, and bias in analysis. We assigned each study a score of up to nine, with higher scores indicating lower risk of bias (appendix p 8).

We assessed the body of evidence as a whole for each outcome using a modified GRADE approach.[34] GRADE scores the certainty of a body of evidence as high, moderate, low, or very low, according to the level of confidence that the estimated effect is close to the true effect. It does so using five criteria: risk of bias in individual studies, inconsistency, indirectness, imprecision, and publication bias. Our scoring criteria follow the same approach as Wolf and colleagues (appendix p 9).[19]

We used random-effects meta-analysis to estimate a pooled relative risk for primary and secondary outcomes, and to estimate the degree of heterogeneity measured by the I^2 statistic. We used metaregression to examine heterogeneity for outcomes with at least ten comparisons.[25] Metaregressions assessed the role of pre-specified covariates, including: handwashing with soap messages being the majority of intervention content, versus the minority (appendix p 2); soap provided, versus not; water supply provided, versus not; domestic settings, versus schools and childcare; randomised studies, versus non-randomised; time of follow-up 12 months or more, versus fewer than 12 months; and studies published before and after 2015. We used the metan and metareg packages in Stata 17 for analysis.

Clustered designs which do not account for clustering in the analysis can have incorrectly estimated standard errors. In theory, the intracluster correlation coefficient (ICC) can be estimated from other studies and used to approximate correct standard errors. However, the ICC depends on many factors, including cluster size.[35] Since many of the incorrectly analysed studies had large cluster sizes, estimating ICCs might introduce more bias than would be removed.[35] Therefore, we did not attempt to correct standard errors of incorrectly analysed studies (22% of comparisons, n=6), instead accounting for this issue in sensitivity analysis and risk of bias scoring.

In subgroup analyses for the primary outcome, we undertook meta-analyses of study results for children younger than 5 years, and for children aged 5–14 years. We undertook sensitivity analyses through further meta-analyses of our primary outcome. First, we excluded studies with quality ratings below the 25th percentile.

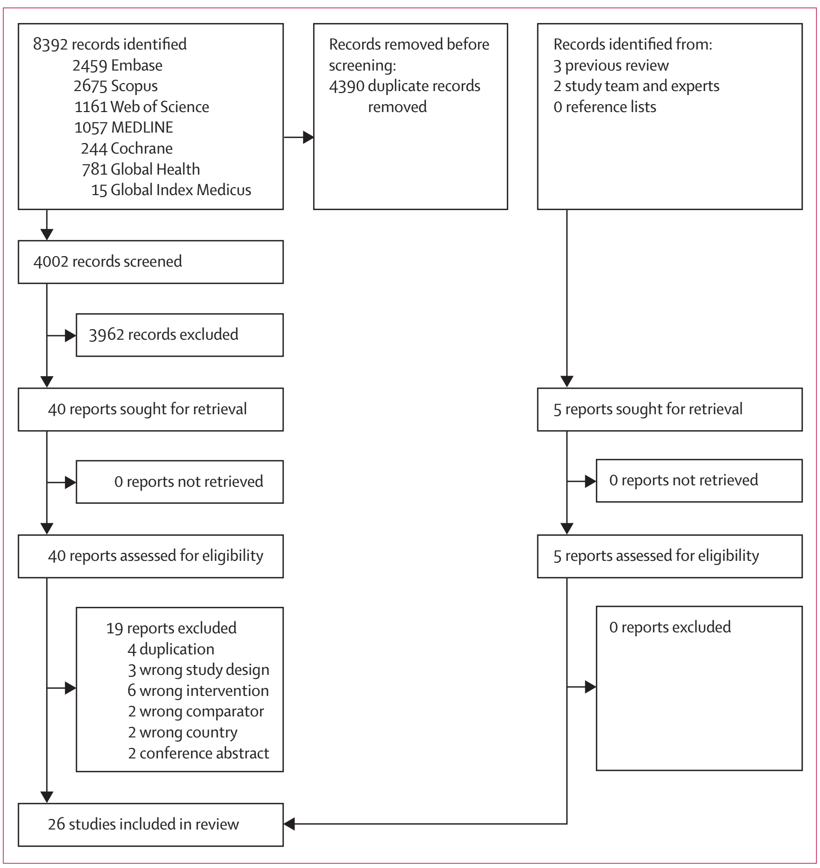

Figure 1: **Study profile**

	Years of study	Country	Milieu	Study design		Intervention	
				Randomisation and study design	Follow-up (months)	HWWS within intervention	Intervention content
Studies in domestic settings (n=18)							
Arnold et al (2009)[41]	2007	Guatemala	Rural	Non-Randomised (PSM)	3	Majority, HWWS ≥50%	Handwashing promotion, alongside household water treatment
Ashraf et al (2020)[31]	2013–15	Bangladesh	Rural	Randomised (cRCT)	24	Majority, HWWS only	Handwashing promotion with soap and HWF provision
Chase and Do (2012)[42]	2009–11	Vietnam	Rural	Randomised (cRCT)	18	Majority, HWWS only	Handwashing promotion
Galiani et al (2015);[33] domestic	2008–11	Peru	Mixed	Randomised (cRCT)	36	Majority, HWWS only	Handwashing promotion
Galiani et al (2015);[33] domestic and schools	2008–11	Peru	Mixed	Randomised (cRCT)	36	Majority, HWWS only	Handwashing promotion
Hartinger et al (2016)[43]	2008–10	Peru	Rural	Randomised (cRCT)	12	Minority	Hygiene promotion including handwashing, alongside cookstove, sink, water connection, SODIS bottles
Huda et al (2012)[44]	2007–09	Bangladesh	Rural	Non-randomised (matched cohort)	24	Minority	Hygiene promotion including handwashing, alongside promotion of sanitation and safe collection and storage of drinking water
Humphrey et al (2019)[39]	2012–15	Zimbabwe	Rural	Randomised (cRCT)	18	Minority	Handwashing promotion with soap and HWF provision, alongside promotion of food hygiene, sanitation, and household water treatment
Hussam et al (2019)[40]*	2015–17	India	Rural	Randomised (cRCT)	8	Majority, HWWS only	Handwashing promotion with soap provision
Luby et al (2005)[15]	2002–03	Pakistan	Urban	Randomised (cRCT)	12	Majority, HWWS only	Handwashing promotion with soap provision
Manaseki-Holland et al (2021)[26]	2015–17	Gambia	Rural	Randomised (cRCT)	32	Majority, HWWS ≥50%	Handwashing promotion with soap provision, alongside food hygiene promotion
Morse et al (2020)[29]	2017–18	Malawi	Rural	Non-randomised (site-randomised)	18	Minority	Hygiene promotion including handwashing, alongside promotion of sanitation and household water management
Najnin et al (2019)[45]	2011–13	Bangladesh	Urban	Randomised (cRCT)	24	Minority	Hygiene promotion including handwashing and HWF provision, alongside household water treatment and cholera vaccine
Nicholson et al (2014)[28]	2007–08	India	Urban	Randomised (cRCT)	10	Majority, HWWS only	Handwashing promotion with soap provision
Pickering et al (2015)[46]	2011–12	Mali	Rural	Randomised (cRCT)	18	Minority	Handwashing promotion alongside sanitation promotion
Ram et al (2015)[47]	2009–10	Bangladesh	Rural	Randomised (cRCT)	1	Majority, HWWS only	Handwashing promotion with soap and HWF provision
Simmerman et al (2011)[48]	2008–09	Thailand	Urban	Randomised (cRCT)	1	Majority, HWWS only	Handwashing promotion with soap provision
Swarthout et al (2020)[32]	2012–16	Kenya	Rural	Randomised (cRCT)	24	Majority, HWWS only	Handwashing promotion with soap and HWF provision
Studies in primary school settings (n=8)							
Bowen et al (2007)[24]	2004–05	China	Mixed	Randomised (cRCT)	5	Majority, HWWS only	Handwashing promotion with soap provision
Chard et al (2019)[49]	2014–17	Laos	Rural	Randomised (cRCT)	24	Minority	Hygiene promotion including handwashing, alongside provision of HWF, sanitation, and water supply and treatment
Galiani et al (2015);[33] domestic and schools	2008–11	Peru	Mixed	Randomised (cRCT)	36	Majority, HWWS only	Handwashing promotion
Mangklakeree et al (2014)[36]	2011	Thailand	Rural	Non-randomised (CBA)	4	Minority	Hygiene promotion including handwashing and cough etiquette, masking, and self-isolation
Patel et al (2012)[38]	2007–09	Kenya	Rural	Non-randomised (controlled cohort)	12	Majority, HWWS ≥50%	Handwashing promotion with soap and HWF provision, alongside promotion and provision of drinking water treatment
Pickering et al (2013)[50]	2010	Kenya	Urban	Randomised (cRCT)	2	Majority, HWWS only	Handwashing promotion with soap and HWF provision
Talaat et al (2011)[23]	2008	Egypt	Urban	Randomised (cRCT)	3	Majority, HWWS only	Handwashing promotion
Trinies et al (2016)[51]	2013–14	Mali	Mixed	Non-randomised (matched cohort)	14	Minority	Handwashing promotion with soap and HWF provision, alongside provision of sanitation and water
Studies in childcare settings (n=2)							
Ban et al (2015)[37]	2010–11	China	Urban	Randomised (cRCT)	12	Majority, HWWS ≥50%	Handwashing promotion with soap and sanitiser provision, alongside surface cleaning
Liu et al (2019)[30]	2015	China	Urban	Randomised (cRCT)	6	Majority, HWWS only	Handwashing promotion with soap provision

CBA=controlled before–after. cRCT=cluster-randomised controlled trial. HWF=handwashing facility. HWWS=handwashing with soap. PSM=propensity score matching in cross-section. SODIS=solar disinfection. *Publicly available as a preprint at time of searches.

Table 1: **Included studies**

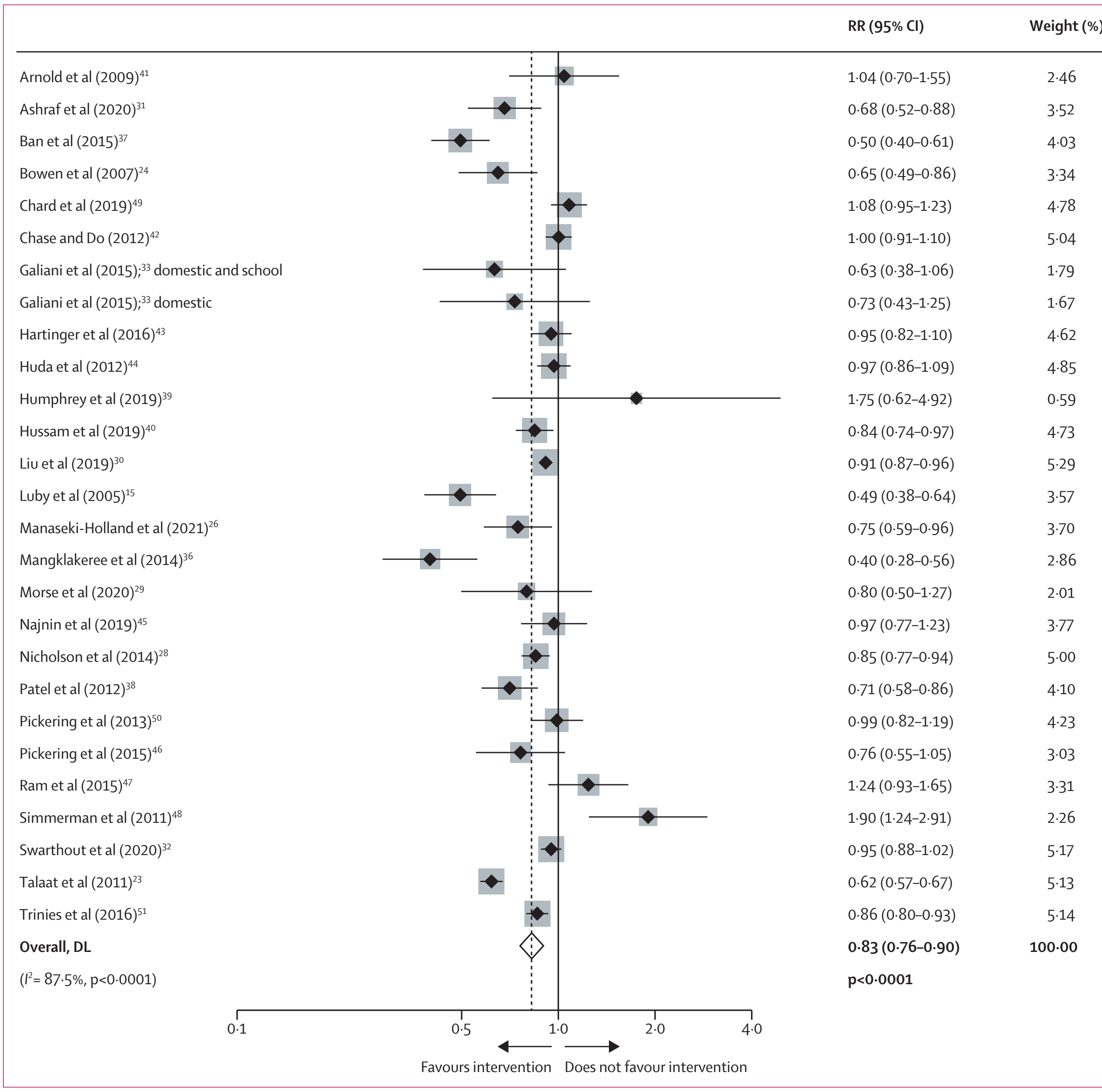

Figure 2: **Forest plot of included comparisons for any acute respiratory infection**
Weights are from random-effects model. DL=DerSimonian and Laird. RR=relative risk.

	Number of comparisons	Effect size (95% CI)	I^2	p value for heterogeneity
Any acute respiratory infection	27	0·83 (0·76–0·90)	88%	<0·0001
Lower respiratory infection	12	0·78 (0·64–0·94)	64%	0·0010
Upper respiratory infection	7	0·74 (0·59–0·93)	91%	<0·0001
Influenza confirmed by diagnostic test	3	0·94 (0·42–2·11)	90%	<0·0001

Table 2: **Pooled estimates of the effect of interventions to promote handwashing versus control for all outcomes**

Second, we excluded non-randomised studies. Third, we included only studies in domestic settings (as opposed to schools and childcare). Fourth, we excluded studies in which handwashing with soap was not the behavioural target for most messages. Fifth, we excluded the six studies[15,28,29,36–38] in which analyses did not adjust for clustering.

This study is registered with PROSPERO, CRD42021231414.

Role of the funding source

The funders had no role in study design, collection and interpretation of data, writing the report, or in the decision to submit for publication.

Results

The search of five electronic databases yielded 8392 records, which was reduced to 4002 after de-duplication (figure 1). By screening the list of included studies of two recent systematic reviews,[16,17] an additional three studies were identified. We included two more studies[39,40] known by the study team to meet inclusion criteria but which had not mentioned ARI terms in their title or abstract. We reviewed full texts of 45 studies, of which 26 met our inclusion criteria. The 26 studies included 161 659 participants, with 13 studies in Asia, nine in Africa, and three in Latin America (table 1). In the appendix (pp 10–12) we provide further study characteristics, such as numbers of participants per group and compliance with promoted behaviours, as well as scores for each risk of bias item (appendix pp 13–15). We also include a list of studies excluded at full text review with primary reason for exclusion (appendix pp 16–17).

For the primary outcome (any ARI), we included 27 comparisons from 26 studies—this included 21 comparisons from randomised studies and six from non-randomised studies. Only two studies reported results by sex.[31,32] Of the 27 interventions included in this review, 18 were conducted in domestic settings, and the remaining nine in primary school or childcare settings. For 18 interventions, handwashing with soap was the behavioural target in the majority of intervention messages, of which 14 had it as the exclusive focus. The remaining nine interventions included multiple broader messages (eg, related to drinking water treatment or mask-wearing; table 1). Soap was provided in 16 interventions.

The primary analysis of 27 comparisons for any ARI provided an RR in favour of handwashing interventions of 0·83 (95% CI 0·76–0·90, I^2 88%; figure 2).

There was limited evidence of publication bias in a funnel plot (appendix p 18), with an Egger test p value of 0·40. The GRADE rating for any ARI was moderate certainty evidence (appendix p 19).

For the outcome of lower respiratory infections, the analysis of 12 comparisons revealed an RR of 0·78 (95% CI 0·64–0·94, I^2 64%; table 2), with moderate certainty evidence. For the outcome of upper respiratory infection, analysis of seven comparisons revealed an RR 0·74 (0·59–0·93, 91%), with low certainty evidence. For the outcome of influenza infection confirmed by diagnostic test, analysis of three comparisons revealed an RR of 0·94 (0·42–2·11, 90%), with very low certainty evidence. No studies meeting the inclusion criteria reported a COVID-19 outcome, and only one reported all-cause mortality (with prevalence ratio of 0·95 [95% CI 0·71–1·27]).[46] Forest plots and GRADE ratings for secondary outcomes are provided in the appendix (pp 19–21).

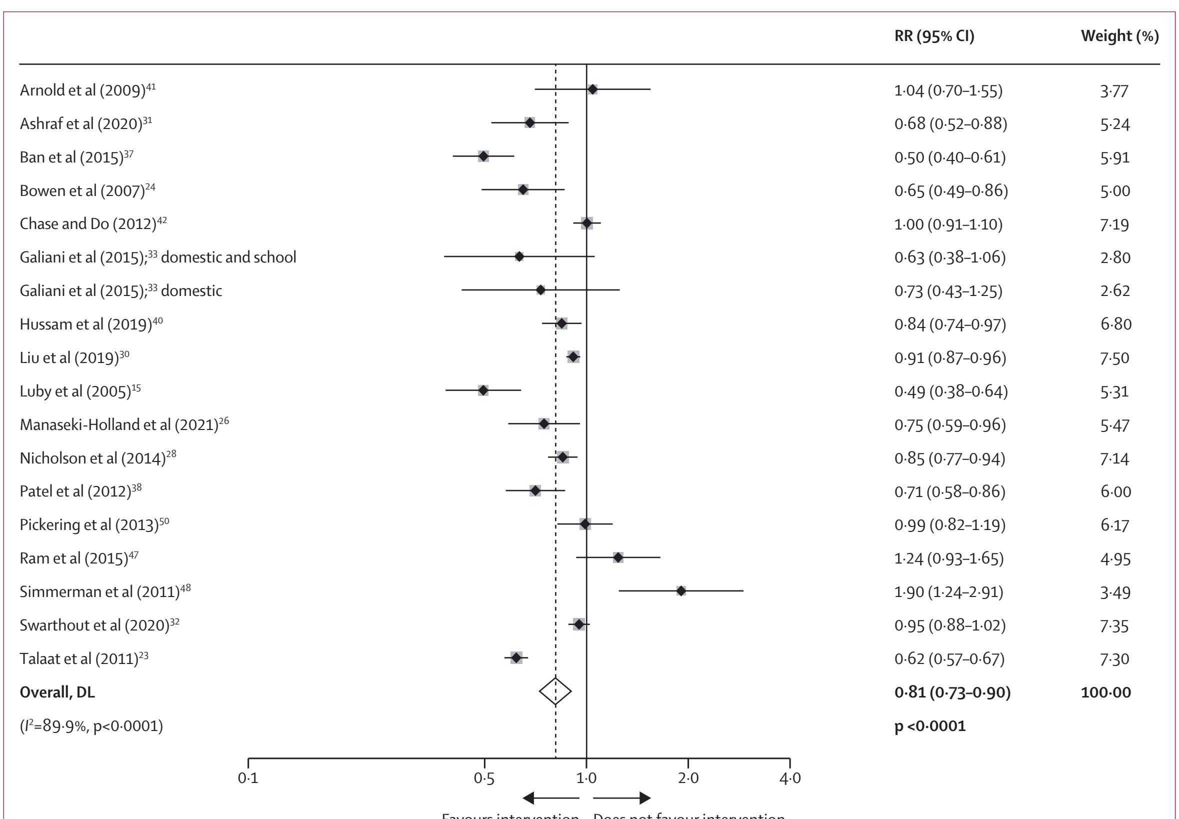

Figure 3: **Forest plot of included comparisons for any acute respiratory infection, for which handwashing comprised the majority of intervention content**
Weights are from random-effects model. DL=DerSimonian and Laird. RR=relative risk.

In metaregression for any ARI there was no evidence (at $p<0\cdot10$) for an association with any of the previously specified covariates (appendix p 24).

When meta-analysis for the primary outcome was restricted to children aged 0–5 years (15 comparisons), the pooled RR for any ARI was 0·82 (0·75–0·90). When restricted to children aged 5–14 years (eight comparisons), the pooled RR for any ARI was 0·76 (0·64–0·90). Only one study provided data for both 0–5 years and 5–14 years subgroup analyses,[28] so these subgroups broadly represent different contexts and interventions.

In a meta-analysis of only randomised studies (21 comparisons), the pooled RR for any ARI was 0·84 (0·76–0·93), which did not reveal considerable deviation from the primary analysis (RR 0·83). When we included only studies with quality ratings above the 25th percentile (21 comparisons), the pooled RR was 0·84 (0·76–0·93). When we included only studies in domestic settings (18 comparisons), the pooled RR was 0·89 (0·81–0·97). When we included only studies in which handwashing was the behavioural target of the majority of messages (18 comparisons), the pooled RR was 0·81 (0·73–0·90; figure 3). When we included only studies that adjusted appropriately for clustering (21 comparisons), the pooled RR was 0·89 (0·82–0·96). Forest plots for sensitivity analyses are in the appendix (pp 21–23).

Discussion

Interventions promoting handwashing with soap reduced ARI morbidity by about 17% (RR 0·83 [95% CI 0·76–0·90]). Such interventions are therefore an important means of preventing ARIs in LMICs, where 83% of ARI mortality occurs.[3] To our knowledge, this study is the first meta-analysis of the effect of handwashing with soap interventions on any ARI since the 2008 study by Aiello and colleagues.[14] Since our estimate for interventions in LMICs is similar in magnitude to the global estimate of Aiello and colleagues (21%) but has greater precision,[10] and is similar to a recent estimate for viral ARI globally (16%),[12] our results are also applicable to HICs.

An LMIC-focused systematic review by McGuinness and colleagues with similar inclusion criteria to ours did not conduct a meta-analysis, but identified 14 randomised studies up to 2017.[16] In our review, we identified 20 randomised studies and six non-randomised studies. Non-randomised intervention studies with appropriate controls bring an increased risk of bias, but provide a broader view of community-based public health interventions which are challenging to evaluate.[52]

Between-study heterogeneity was relatively high by the standards of clinical interventions, and we were able to explain it only partly via metaregression. This high heterogeneity might be expected for interventions reliant on uptake and adherence to behaviours, and for studies employing various strategies with different durations and intensities.[53] For example, I^2 statistics were higher than 60% for many meta-analyses within recent Cochrane reviews of interventions such as medical masks to prevent viral illness[12] and indoor residual spraying for malaria.[54] Observed heterogeneity might be partly due to the variety in promotional approaches, follow-up periods, and case definitions. Alternatively, high heterogeneity might also reflect missing influential covariates in multiple studies or measurement error, factors which would also affect the magnitude of effect estimates.

A strength of our study is in using transparent aggregation of different symptoms and case definitions to construct broader outcomes for meta-analysis.[27] Had we only conducted meta-analyses on identical case definitions,[16] this would artificially understate the extent of the evidence. A further strength is in distinguishing between lower and upper respiratory infections, which previous handwashing meta-analyses have not done. The RR 95% CIs for lower and upper respiratory infections overlap substantially, and are similar to that for any ARI (table 2). The 95% CIs for test-confirmed influenza overlaps 1, but our estimate was based on only three comparisons. Two of these studies[47,48] assessed interventions delivered to household members of a confirmed influenza case, and were probably delivered too late to prevent domestic transmission. The third study[23] was in a general population of schoolchildren and did identify an effect on test-confirmed influenza (appendix p 21). We identified no intervention studies with a COVID-19 outcome, in line with a meta-analysis of public health measures and COVID-19, which identified only studies assessing associations with self-reported handwashing.[55]

Limitations of the evidence we assessed include risks of bias inherent in the original study designs. First, masking of participants in handwashing interventions is impossible. Second, symptoms included in our primary outcome were typically caregiver-reported or self-reported.[56] In our lower respiratory infection analysis, however, five of 12 comparisons were for more objective outcomes (watch-timed rapid respiratory rate), with a similar pooled RR to the primary outcome. Nonetheless, risk of bias remains if outcome measurement staff were not masked to allocation, as in almost all studies (appendix pp 13–15). Reporting bias could therefore lead to effects being overstated, but any overestimate might be offset by factors such as less-than-full participation in interventions by the target population (ie, exposure misclassification) or low compliance. Of the seven studies that used structured observations of behaviour as opposed to self-report,[57] four saw improvements at some crucial times, but not others (appendix pp 10–12). Limitations of our review processes include that we did not systematically search grey literature, so studies not published in indexed journals might have been omitted.

For effective uptake of handwashing with soap, complementary investments are required in water supply and handwashing facilities, which can be costly to households and governments.[58] Hand hygiene is best facilitated by a water supply on premises, but 27% of the LMIC population (1·8 billion people) do not have such a service.[11] Furthermore, nearly a third of the global population, almost exclusively in LMICs, does not have a handwashing facility with soap and water at home.[11]

As in previous outbreaks of avian and swine influenza, most governments have promoted handwashing with soap during the COVID-19 pandemic.[59] However, in comparison with the attention given to handwashing during these epidemics of respiratory disease, handwashing campaigns in normal times are rare. Our review suggests that the scarcity of such campaigns might be a missed opportunity, and promoting handwashing with soap more broadly could reduce the large endemic burden of respiratory disease.

Contributors

IR contributed to conceptualisation, literature search, data accessed and verified, data analysis, data interpretation, writing—original draft, writing—review and editing, and the decision to submit. SB contributed to the literature search, data accessed and verified, data analysis, data interpretation, and writing—review and editing. PA, RD, JW, MCF, and EA contributed to conceptualisation, writing—review and editing. MB contributed to data interpretation and writing—review and editing. OC contributed to conceptualisation, data accessed and verified, data interpretation, writing—review and editing, supervision, and decision to submit.

Declaration of interests

IR and SB report grants from the Reckitt Global Hygiene Institute during the conduct of the study. OC reports grants from the UK Foreign, Commonwealth, and Development Office (FCDO) and the Bill & Melinda Gates Foundation during the conduct of the study. JW reports grants from UK FCDO during the conduct of the study. MB reports grants from the Bill & Melinda Gates Foundation during the conduct of the study. RD reports a donation from Reckitt, outside the submitted work. MCF reports consulting fees from Reckitt, outside the submitted work. All other authors declare no competing interests.

Data sharing

Study data used in meta-analysis and analytical code are available at https://osf.io/3ef5y/.

Acknowledgments

We thank authors of included studies who responded to requests for more information. Some authors are staff members of WHO. The authors alone are responsible for the views expressed in this publication, which do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated. IR was supported by the Bill & Melinda Gates Foundation and the Reckitt Global Hygiene Institute. OC was supported by the Bill & Melinda Gates Foundation and the UK Foreign, Commonwealth, and Development Office. SB was supported by the Reckitt Global Hygiene Institute.

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