WHAT IS ALREADY KNOWN ON THIS TOPIC

Inhaled nitric oxide continues to be used to improve oxygenation in patients with acute lung injury, despite no clear supporting evidence

A previous meta-analysis in 2003 included five randomised trials of nitric oxide; there are now 12 trials

WHAT THIS STUDY ADDS

Nitric oxide improves oxygenation temporarily but does not improve survival and may cause harm

We do not recommend routine use of nitric oxide in patients with acute lung injury

In conclusion, our systematic review and meta-analysis found that inhaled nitric oxide improved oxygenation in patients with ALI and ARDS with 24 hours of therapy, with some evidence for a more prolonged effect. Given that the best available evidence suggests no survival advantage and possible increased mortality and renal dysfunction with nitric oxide, we do not recommend its routine use.

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Interventions to improve water quality for preventing diarrhoea: systematic review and meta-analysis

Thomas Clasen,[1] Wolf-Peter Schmidt,[1] Tamer Rabie,[3] Ian Roberts,[2] Sandy Cairncross[1]

EDITORIAL by Luby

[1]Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London WC1E 7HT
[2]Department of Epidemiology and Public Health, London School of Hygiene and Tropical Medicine
[3]World Bank, Washington, DC, USA

Correspondence to: T Clasen
thomas.clasen@lshtm.ac.uk

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ABSTRACT

Objective To assess the effectiveness of interventions to improve the microbial quality of drinking water for preventing diarrhoea.

Design Systematic review.

Data sources Cochrane Infectious Diseases Group's trials register, CENTRAL, Medline, Embase, LILACS; hand searching; and correspondence with experts and relevant organisations.

Study selection Randomised and quasi-randomised controlled trials of interventions to improve the microbial quality of drinking water for preventing diarrhoea in adults and in children in settings with endemic disease.

Data extraction Allocation concealment, blinding, losses to follow-up, type of intervention, outcome measures, and measures of effect. Pooled effect estimates were calculated within the appropriate subgroups.

Data synthesis 33 reports from 21 countries documenting 42 comparisons were included. Variations in design, setting, and type and point of intervention, and variations in defining, assessing, calculating, and reporting outcomes limited the comparability of study results and pooling of results by meta-analysis. In general, interventions to improve the microbial quality of drinking water are effective in preventing diarrhoea. Effectiveness was not conditioned on the presence of improved water supplies or sanitation in the study setting and was not enhanced by combining the intervention with instructions on basic hygiene, a water storage vessel, or improved sanitation or water supplies—other common environmental interventions intended to prevent diarrhoea.

Conclusion Interventions to improve water quality are generally effective for preventing diarrhoea in all ages and in under 5s. Significant heterogeneity among the trials suggests that the level of effectiveness may depend on a variety of conditions that research to date cannot fully explain.

INTRODUCTION

Reviews of environmental interventions to prevent diarrhoeal disease reported a 15-17% median reduction in diarrhoea from water quality interventions,[1 2] yet the included studies concerned improvements at the water source and none at

other points of use, or at the household where recontamination can occur.[3]

We report updated results of a systematic review undertaken with the Cochrane Collaboration on interventions to improve the microbial quality of drinking water for preventing diarrhoea.[4]

METHODS

We searched for randomised and quasi-randomised controlled trials of interventions to improve water quality for the prevention of diarrhoea (see bmj.com). Interventions included any measure to improve the microbial quality of drinking water. The primary outcome was diarrhoea related morbidity. We present results separately according to the reported measures of effect (risk ratios, rate ratios, odds ratio, longitudinal prevalence ratios).

For randomised controlled trials we assessed methodological quality on the basis of established criteria.[5] For quasi-randomised trials we assessed the comparability of intervention and control groups at baseline for water quality, diarrhoeal morbidity, age, socioeconomic status, access to water, hygiene practices, and sanitation facilities, and whether data collection for the groups was contemporaneous.

We calculated pooled estimates using a random effects inverse variance method.[5] Heterogeneity was examined (Forest plots, χ^2 test, I^2 statistic). Factors considered as potential explanations for heterogeneity were age (all *v* under 5s), point of intervention (water source *v* household), type of intervention, compliance (<50% *v* ≥50%), and effectiveness under various conditions for water supply, sanitation, and access (see bmj.com). We included all intervention arms in the meta-analysis even when two or more were compared against one control.

RESULTS

Overall 976 potentially relevant studies of interventions to improve water quality for preventing diarrhoea were identified (see bmj.com). Thirty three (22 randomised controlled, 11 quasi-randomised controlled) with 42

Summary of pooled estimates (random effects) for studies reporting rate ratios, risk ratios, longitudinal prevalence ratios, and odds ratios for all studies (source based and household based), by point of intervention (source or household), and by type of household water treatment (chlorination, filtration, solar disinfection, and flocculation-disinfection)

	All ages				Under 5s			
Measure of effect and intervention	No of trials	Pooled estimate* (95% CI)	Probability of heterogeneity†	Consistency‡ (%)	No of trials	Pooled estimate* (95% CI)	Probability of heterogeneity†	Consistency‡ (%)
Rate ratios								
All	12	0.75 (0.65 to 0.87)§	<0.0001	92.3	8	0.81 (0.69 to 0.95)	0.0001	92.2
Source based	4	0.87 (0.74 to 1.02)	0.0002	85.1	3	0.93 (0.82 to 1.05)	0.17	44.3
Household based:	8	0.62 (0.47 to 0.82)§	0.0001	88.9	5	0.70 (0.54 to 0.89)	0.0001	86.8
Chlorination	4	0.61 (0.46 to 0.81)§	0.01	72.8	2	0.53 (0.23 to 1.23)	0.002	89.4
Filtration	3	0.56 (0.25 to 1.27)	0.003	83.2	2	0.51 (0.11 to 2.37)	0.004	88.1
Solar disinfection	1	0.64 (0.41 to 1.00)	NA	NA	1	0.64 (0.41 to 1.00)	NA	NA
Risk ratios								
All	8	0.50 (0.41 to 0.61)§	0.0001	85.7	6	0.61 (0.48 to 0.77)§	0.13	40.8
Source based	1	0.45 (0.43 to 0.47)	NA	NA	0	NA	NA	NA
Household based:	7	0.49 (0.36 to 0.65)§	0.002	71.8	6	0.61 (0.48 to 0.77)§	0.13	40.8
Chlorination	4	0.41 (0.26 to 0.65)	0.003	78.4	3	0.60 (0.41 to 0.87)	0.06	64.7
Filtration	2	0.41 (0.21 to 0.79)§	0.66	0	2	0.41 (0.21 to 0.79)§	0.66	0
Improved storage	1	0.79 (0.61 to 1.03)	NA	NA	1	0.69 (0.47 to 1.01)	NA	NA
Longitudinal prevalence ratios								
All	11	0.56 (0.27 to 1.16)§	0.0001	98.8	11	0.61 (0.29 to 1.26)§	0.0001	99.0
Source based	1	0.56 (0.37 to 0.84)	NA	NA	1	0.63 (0.49 to 0.81)	NA	NA
Household based:	10	0.56 (0.25 to 1.23)§	0.0001	98.9	10	0.60 (0.27 to 1.36)§	0.0001	99.1
Chlorination	5	0.82 (0.60 to 1.11)§	0.04	60.4	5	0.91 (0.82 to 1.02)§	0.75	0
Flocculation-disinfection	5	0.40 (0.14 to 1.16)§	0.0001	98.9	5	0.42 (0.13 to 1.37)§	0.0001	99.2
Odds ratios								
All	10	0.65 (0.56 to 0.76)§	0.0005	69.7	7	0.65 (0.46 to 0.91)§	0.004	69.0
Household based:	10	0.65 (0.56 to 0.76)§	0.0005	69.7	7	0.65 (0.46 to 0.91)§	0.004	69.0
Chlorination	3	0.77 (0.58 to 1.02)§	0.08	59.5	2	0.90 (0.65 to 1.25)§	0.74	0
Filtration	3	0.37 (0.27 to 0.49)	0.49	0	3	0.37 (0.22 to 0.62)	0.23	32.5
Solar disinfection	2	0.69 (0.63 to 0.74)	0.76	0	0	NA	NA	NA
Flocculation-disinfection	2	0.77 (0.65 to 0.90)§	0.70	0	2	0.86 (0.57 to 01.29)§	0.06	72.1

NA=not applicable.
*For single studies, estimate is from that study only.
†χ^2.
‡I^2.
§Includes studies with multiple intervention arms compared with a single control so that statistical significance of these analyses must be interpreted with caution.

comparisons and totalling 55 650 participants met the inclusion criteria (see bmj.com).[w1-w33] Six studies had two or more intervention arms. This paper includes three new studies not in the original review.[w6 w9 w29]

Interventions to improve water quality were undertaken at the water source (n=7 trials) or household (n=35). Source based interventions included protected wells, bore holes, or distribution to public tap stands. Household interventions comprised improved water storage (n=1) or treating water at home by chlorination (n=16), solar disinfection (n=3), filtration (n=8), or flocculation-disinfection (n=7).

Effectiveness

The forest plots for studies reporting effect estimates for all ages and for under 5s are on bmj.com. Evidence from the pooled estimates of effect suggests that interventions to improve the microbial quality of water are effective in reducing the occurrence of diarrhoea for all ages and for under 5s (table). Pooled estimates, however, showed heterogeneity (table).

Exploring heterogeneity

Although trials of source based interventions reported the intervention to be effective, the pooled estimate for trials using rate ratios fell short of statistical significance (all ages (n=4), 0.87, 95% confidence interval 0.74 to 1.02; under 5s (n=3), 0.93, 0.82 to 1.05: table). The two studies on source based interventions reporting the highest level of effectiveness could not be pooled because they used different measures of effect[w24 w33]; the small number of clusters and failure to account for clustering raises doubts about the validity of such estimates. Household interventions, however, significantly reduced diarrhoea episodes among all ages and among under 5s, as measured with rate ratios, risk ratios, and odds ratios, but pooled estimates were heterogeneous. The pooled longitudinal prevalence ratio for household interventions was statistically significant when a possible outlier[w13] was excluded for all ages (0.70, 0.56 to 0.88; n=9) and for under 5s (0.76, 0.66 to 0.88; n=9).

Although subgrouping by household intervention reduced heterogeneity among certain types of interventions other pooled estimates still showed heterogeneity (table). Chlorination was associated with a statistically significant reduction in diarrhoea among all ages when measuring rate ratios and risk ratios, and in under 5s when measuring risk ratios. Filters were associated with a statistically significant and homogeneous reduction in diarrhoea among all ages and in under 5s when measuring risk ratios and odds ratios, but not when measuring rate ratios. Excluding the two US studies in settings with high ambient water quality[w8 w9] resulted in a statistically significant rate ratio in favour of the intervention in one study (0.21, 0.07 to 0.61). Solar disinfection was associated with a reduction in diarrhoea among all ages in both trials measuring odds ratios. A single study that measured the effectiveness of the intervention among under 5s reported a rate ratio of 0.64 (0.41 to 1.00). For flocculation-disinfection, pooled estimates from the five trials reporting longitudinal prevalence ratios found no statistically significant difference in the number of diarrhoea episodes compared with the control, either for all ages or for under 5s. Excluding a possible outlier,[w13] however, rendered the pooled estimate statistically significant in favour of the intervention (all ages, 0.60, 0.43 to 0.83; under 5s, 0.66, 0.43 to 0.76). The two trials using odds ratios reported a statistically significant reduction in diarrhoea episodes for all ages from flocculation-disinfection but not for under 5s. The one trial of improved storage found a protective but, lacking power, not statistically significant difference in diarrhoea episodes, measured with risk ratios (all ages, 0.79, 0.61 to 1.03; under 5s, 0.69, 0.47 to 1.01).[w28]

Among trials reporting odds ratios, the pooled estimate of effect was substantially higher in settings where compliance was higher (≥50% compliance (n=4), odds ratio 0.39, 0.39 to 0.51 *v* <50% compliance (n=4), 0.80, 0.71 to 0.89). The trials for the last category were from one study[w27] and were compared with only one control group.

No statistically significant differences were found between pooled estimates on the basis of water supply being "improved" or "unimproved." Pooled estimates, however, showed a statistically significant effect in favour of intervention even in settings without improved water supply (reported rate ratios (n=7), 0.74, 0.63 to 0.87; risk ratios (n=4), 0.46, 0.36 to 0.58; longitudinal prevalence ratios (n=6), 0.83, 0.68 to 1.01; and odds ratios (n=9), 0.66, 0.57 to 0.77). Interventions were also effective in settings without improved sanitation (rate ratios (n=4), 0.78, 0.64 to 0.95; risk ratios (n=2), 0.55, 0.47 to 0.65).

Pooled estimates showed that water quality interventions were significantly effective alone or with other environmental interventions. No evidence was found for water quality interventions being more effective when combined with other components. Pooled estimates for water quality interventions alone (odds ratios (n=7), 0.61, 0.50 to 0.73; rate ratios (n=5), 0.76, 0.52 to 1.02) were not statistically different from pooled estimates for trials combining water quality either with instruction on basic hygiene (odds ratio (n=1), 0.52, 0.30 to 0.90; rate ratios (n=3), 0.85, 0.70 to 1.03), with a storage vessel (odds ratios (n=3), 0.77, 0.58 to 0.84; rate ratios (n=4), 0.61, 0.46 to 0.81), with sanitation (odds ratios (n=3), 0.60, 0.43 to 0.84; rate ratio (n=1), 0.75, 0.70 to 0.80), or with improved water supply (odds ratios (n=4), 0.70, 0.59 to 0.84; rate ratios (n=2), 0.77, 0.71 to 0.84).

Subgrouping trials on study design did not show a trend in favour of either (see bmj.com). Greater protective effects were generally reported among randomised controlled trials with high quality for sequence generation, allocation concealment, and inclusion or losses to follow-up. Only four studies used double blinding (table) and none found a statistically significant protective effect from the water quality intervention.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Water that is safe at the point of collection often becomes contaminated with faeces during transport, use, and storage in the home

WHAT THIS STUDY ADDS

Interventions to improve the microbial quality of water are effective for preventing diarrhoea

The interventions were effective in people of all ages and in under 5s

DISCUSSION

This systematic review of 42 controlled trials among some 56 000 participants shows that interventions to improve the microbial quality of drinking water are effective in reducing the occurrence of diarrhoea in all ages.

Pooled estimates from 12 studies reporting rate ratios suggest that household based interventions are more effective at preventing diarrhoea than water source based ones. Such estimates, however, exclude the results from the two studies of source based interventions that reported the highest level of effectiveness and achieved results equivalent to the household based interventions using the same measure of effect.[w24 w33] Evidence was also found for effectiveness being related to compliance. Water quality interventions were effective in reducing diarrhoea even without improved water supplies and sanitation. Effectiveness did not seem to be enhanced by combining the intervention with common preventive strategies.

Many of the included trials were quasi-randomised and failed to take all the steps to avoid bias. In subgroup analyses, however, trials of higher quality for allocation concealment showed a greater overall level of effectiveness. Only four of the 22 randomised controlled studies were properly blinded, and no statistically significant protective effect was found among such blinded trials.[w2 w8 w9 w19]

Trials of household interventions tended to be research driven, whereas those of source based interventions were often evaluations of programmes. Trials of source based interventions were nearly six times as long as those of household ones. Seasonality is important and failure to include data for at least 12 months may have influenced the estimates of effect.[6] A scatter plot of trial duration against effectiveness showed no association.

Source based interventions are often primarily designed to improve water quantity, which may be a separate and possibly more significant contributor to health.[7] Most trials of household interventions were in settings with sufficient water, which may affect the generalisability of these results to locations with inadequate water supplies.

Household interventions require effort on the part of householders to treat their water correctly and consistently, avoid recontamination, and refrain from drinking from untreated sources. Each of these creates an opportunity for non-compliance, which reduces effectiveness. Most source based interventions extend to the household's entire water supply without any additional steps for compliance on the part of the intervention population.

Ultimately the value of water quality interventions in preventing diarrhoeal disease depends not only on their effectiveness but also on their affordability, acceptability, sustainability, and scalability within a vulnerable population.

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Endpiece
Aristotle: clinical epidemiologist?

None of the arts theorise about individual cases. Medicine, for instance, does not theorise about what will help to cure Socrates or Callias, but only about what will help to cure any or all of a given class of patients. This alone is business: individual cases are so infinitely various that no systematic knowledge of them is possible. Aristotle. *Rhetoric.* book I, chapter 2: 1356b

Submitted by Klaus Witt, *assistant professor, Department of General Practice, University of Copenhagen*