

Physical interventions to interrupt or reduce the spread of respiratory viruses: systematic review

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BMJ 2008;336:77-80
doi:10.1136/bmj.39393.510347.BE

This article is an abridged version of a paper that was published on bmj.com on 27 November 2007. Cite this article as: *BMJ* 27 November 2007, doi: 10.1136/bmj.39393.510347.BE.

ABSTRACT

Objective To systematically review evidence for the effectiveness of physical interventions to interrupt or reduce the spread of respiratory viruses.

Data extraction Search strategy of the Cochrane Library, Medline, OldMedline, Embase, and CINAHL, without language restriction, for any intervention to prevent transmission of respiratory viruses (isolation, quarantine, social distancing, barriers, personal protection, and hygiene). Study designs were randomised trials, cohort studies, case-control studies, and controlled before and after studies.

Data synthesis Of 2300 titles scanned 138 full papers were retrieved, including 49 papers of 51 studies. Study quality was poor for the three randomised controlled trials and most of the cluster randomised controlled trials; the observational studies were of mixed quality.

Heterogeneity precluded meta-analysis of most data except that from six case-control studies. The highest quality cluster randomised trials suggest that the spread of respiratory viruses into the community can be prevented by intervening with hygienic measures aimed at younger children. Meta-analysis of six case-control studies suggests that physical measures are highly effective in preventing the spread of SARS: handwashing more than 10 times daily (odds ratio 0.45, 95% confidence interval 0.36 to 0.57; number needed to treat=4, 95% confidence interval 3.65 to 5.52); wearing masks (0.32, 0.25 to 0.40; NNT=6, 4.54 to 8.03); wearing N95 masks (0.09, 0.03 to 0.30; NNT=3, 2.37 to 4.06); wearing gloves (0.43, 0.29 to 0.65; NNT=5, 4.15 to 15.41); wearing gowns (0.23, 0.14 to 0.37; NNT=5, 3.37 to 7.12); and handwashing, masks, gloves, and gowns combined (0.09, 0.02 to 0.35; NNT=3, 2.66 to 4.97). The incremental effect of adding virucidals or antiseptics to normal handwashing to decrease the spread of respiratory disease remains uncertain. The lack of proper evaluation of global measures such as screening at entry ports and social distancing prevent firm conclusions being drawn.

Conclusion Routine long term implementation of some physical measures to interrupt or reduce the spread of respiratory viruses might be difficult but many simple and low cost interventions could be useful in reducing the spread.

INTRODUCTION

High viral load and high infectiousness probably drive virus pandemics.¹ Evidence suggests, however, that single measures, particularly the use of vaccines or antivirals, will be insufficient to interrupt the spread of influenza, and agent specific drugs are not available for other viruses.¹⁻⁴

We systematically reviewed the evidence for the effectiveness of combined public health measures such as personal hygiene, distancing, and barriers to interrupt or reduce the spread of respiratory viruses.^{5,6}

METHODS

We considered trials, observational studies, and other comparative designs in people of all ages provided attempts had been made to control for confounding.

We included any intervention to prevent the transmission of respiratory viruses (isolation, quarantine, social distancing, barriers, personal protection, and hygiene) compared with no intervention or with another intervention.

The outcome measures were deaths; numbers of cases of viral illness; severity of viral illness, or proxies for these; and other measures of burden, such as admissions to hospital.

Several databases (see bmj.com for search terms) were searched, with no language restrictions, and the references of included studies scanned to identify other potentially relevant studies.

We scanned the titles and abstracts of potentially relevant studies: when they seemed to meet our eligibility criteria, we obtained the full text articles. Eligibility of each study was assessed on the basis of the full article.

We analysed randomised and non-randomised studies separately. Randomised studies were assessed according to the effectiveness of the randomisation method, the generation of the allocation sequence, allocation concealment, blinding, and follow-up. Non-randomised studies were assessed for the presence of potential confounders using the Newcastle-Ottawa Scales⁷ for case-control and cohort studies, and a three point checklist for controlled before and after studies.⁸

We assigned risk of bias categories on the basis of the number of items judged inadequate in each study: low risk, up to one inadequate item; medium risk, up to three inadequate items; and high risk, more than three inadequate items.

Aggregation of data depended on study design; types of comparisons; sensitivity; and homogeneity of definitions of exposure, populations, and outcomes used. We used the statistic I^2 for each pooled estimate to assess heterogeneity.^{9,10}

When possible we did a quantitative analysis and summarised effectiveness as odds ratios with 95% confidence intervals, expressing absolute intervention effectiveness when significant as a percentage (intervention

effectiveness=1–odds ratio). For studies that could not be pooled we used effect measures reported by the authors. We calculated numbers needed to treat (NNT) whenever we thought the data were robust enough to allow it.

RESULTS

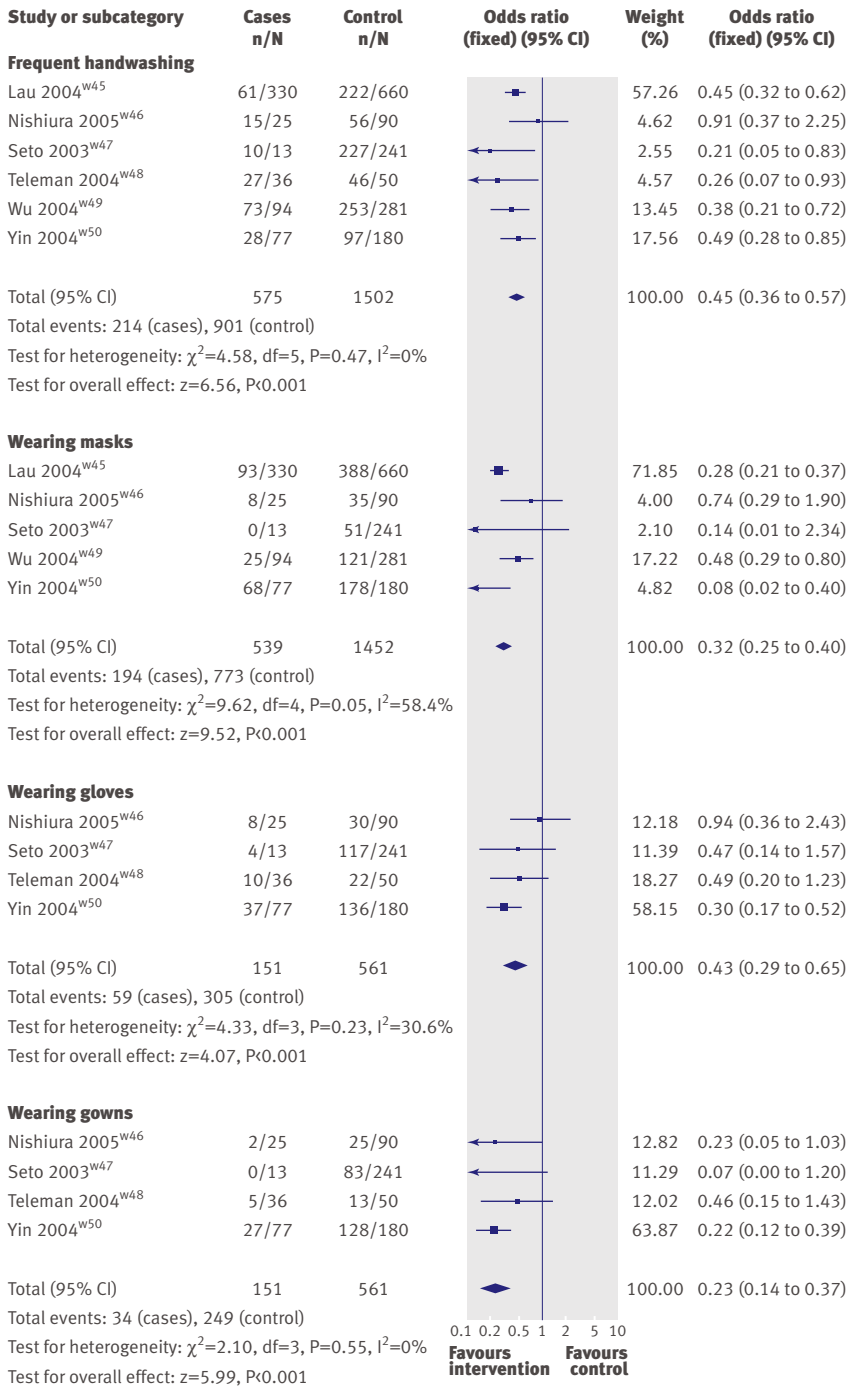
Overall, 2300 titles of reports of potentially relevant studies were identified and screened. In total, 2162 were excluded and 138 full papers retrieved, totalling 49 reports of 51 studies (see bmj.com).

The quality of the methods of included studies^{w1-w51} varied (see bmj.com). Considerable loss of information resulted from incomplete or no reporting of randomisation,^{w3} blinding,^{w5} numerators and denominators,^{w4 w6} interventions, outcomes,^{w39} attrition of participants,^{w34} confidence intervals,^{w33} and cluster coefficients.^{w4} The impact of potential biases such as cash incentives were not discussed. Some authors confused the cohort design with a before and after design, which provided conclusions unsupported by the data.^{w34} Method quality was sometimes eroded by the need to deliver behavioural interventions with service delivery.^{w37} Even when sub-optimal designs were selected, authors rarely articulated potential confounders. A common confounder specific to this area is the huge variability in viral incidence over time, commonly ignored.^{w19 w41} Sometimes this was tackled in the study design.^{w30} Inadequate blinding or adjustment for confounders is well known to exaggerate the effects of interventions.¹¹

Inappropriate interventions for comparison caused problems with study designs: in some studies these probably diluted the intervention outcome^{w9}; in two studies blinding may have failed because placebo handkerchiefs were impregnated with a dummy compound that stung the users' nostrils.^{w3} Some interventions were impractical: participants allocated to the intervention hand cleaner (organic acids) were not allowed to use their hands between cleaning and challenge with virus,^{w3} and 2% aqueous iodine is a successful antiviral intervention when painted on the hands but it stains.^{w51} Compliance with interventions—especially educational programmes—was problematic for several studies.

The most impressive effects came from high quality cluster randomised trials in preventing the spread of respiratory virus in younger children using hygienic measures. One study reported a significant decrease in respiratory illness in children up to age 24 months (relative risk 0.90, 95% confidence interval 0.83 to 0.97), although the decrease was not significant in older children (0.95, 0.89 to 1.01).^{w11}

Six case-control studies assessed the impact of public health measures to curb the spread of SARS in China, Singapore, and Vietnam in 2003. Homogeneity of case definition, agent, settings, and outcomes made meta-analysis possible, using a fixed effects model because no comparisons showed significant heterogeneity (figure and bmj.com). Only binary data were pooled despite the availability of continuous data, because the variables differed or were measured in different units, and standard deviations were usually missing. The data suggest that



Evidence from case-control studies on effect of frequent handwashing or wearing of masks, gloves, or gowns on prevention of severe respiratory syndrome (SARS)

WHAT IS ALREADY KNOWN ON THIS TOPIC

People are increasingly concerned about pandemics of virus infections such as avian influenza and SARS

Preparation against pandemics includes developing vaccines and stockpiling antiviral agents—interventions that are virus specific and of unknown effectiveness in epidemic disease

WHAT THIS STUDY ADDS

Several physical barriers, especially handwashing, masks, and isolation of potentially infected people, were effective in preventing the spread of respiratory virus infections

Such interventions should be better evaluated and given higher priority in preparation for pandemics

implementing barriers to transmission, isolation, and hygienic measures are effective and relatively cheap to contain epidemics of respiratory viruses, with estimates of effect ranging from 55% to 91%: washing hands more than 10 times daily (odds ratio 0.45, 95% confidence interval 0.36 to 0.57, NNT=4, 95% confidence interval 3.65 to 5.52); wearing masks (0.32, 0.25 to 0.40, NNT=6, 4.54 to 8.03); wearing N95 masks (0.09, 0.03 to 0.30, NNT=3, 2.37 to 4.06); wearing gloves (0.43, 0.29 to 0.65, NNT=5, 4.15 to 15.41); wearing gowns (0.23, 0.14 to 0.37, NNT=5, 3.37 to 7.12); and handwashing, masks, gloves, and gowns combined (0.09, 0.02 to 0.35, NNT=3, 2.66 to 4.97). All studies selected hospital cases, except one^{w45} in which the cases were people with probable SARS. Evidence was limited for the superior effectiveness of barrier devices to droplets such as the N95 respirator masks^{w48} over simple surgical masks. An incremental effect was found for decreased burden of respiratory disease by adding virucidals or antiseptics to handwashing in atypical settings, but the extra benefit may have been from confounding additional routines.

Studies on interventions to prevent the transmission of respiratory syncytial virus and similar viruses in more typical settings suggested good effectiveness, although the findings were doubtful because of method quality inherent in controlled before and after studies.

Few studies reported on resource consumption for the physical intervention evaluated. One case-control study^{w45} concluded that handwashing needs to be carried out more than 10 times daily to be effective, whereas a study^{w25} in a military training setting concluded more than four times daily.

Proper evaluation of global and resource intensive measures such as screening at entry ports and social distancing was lacking. The handful of studies (mostly during the SARS epidemic) did not allow firm conclusions to be drawn.

DISCUSSION

In this systematic review we found that physical barriers such as handwashing, wearing a mask, and isolation of potentially infected patients were effective in preventing the spread of respiratory virus infections. It is not surprising that the included studies were at risk of bias as such interventions are difficult to blind, are often set up hurriedly in emergency situations, and funding is less secure than for profit making interventions. Inadequate

reporting often made interpretation of before and after studies difficult.

The settings of the studies, carried out over four decades, were heterogeneous. Few attempts were made to obtain socioeconomic diversity. We identified few studies from developing countries where the most burden lies and where cheap interventions are needed.

Compliance with interventions—especially educational programmes—was a problem for several studies, despite the importance of such low cost interventions. Routine long term implementation of some would be problematic—particularly maintaining strict hygiene and barrier routines for long periods.

Global and highly resource intensive measures such as screening at entry ports and social distancing lacked proper evaluation. The handful of studies (mostly done during the SARS epidemic) did not allow us to reach any firm conclusions, although a recent analysis suggests an effect of social distancing measures such as school closures and bans on public gatherings.¹²

Nevertheless, our systematic review of available research does provide some important insights. Perhaps the impressive effect of the hygienic measures aimed at younger children derives from their poor capability with personal hygiene.^{w1 w11}

Simple public health measures seem to be highly effective at reducing the transmission of respiratory viruses, especially when they are part of a structured programme including instruction and education and when they are delivered together. Further large pragmatic trials are needed to evaluate the best combinations. In the meantime to reduce the transmission of respiratory viruses we recommend implementing frequent handwashing, barrier measures (gloves, gowns, and masks), and isolation of people with suspected respiratory tract infections.

We thank Peter Doshi, Anne Lyddiatt, Stephanie Kondos, Tom Sandora, Kathryn Glass, Max Bulsara, and Allen Cheng for commenting on the draft protocol; Jørgen Lous for translating a Danish paper and extracting data; Taixiang Wu for translating Chinese text; and Ryuki Kassai for translating Japanese text.

Contributors: See bmj.com.

Funding: Cochrane Collaboration Steering Group, UK, and each author's institution.

Competing interests: None declared.

Ethical approval: Not required.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Accepted: 23 October 2007

Chloramphenicol versus ampicillin plus gentamicin for community acquired very severe pneumonia among children aged 2-59 months in low resource settings: multicentre randomised controlled trial (SPEAR study)

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BMJ 2008;336:80-4

doi:10.1136/bmj.39421.435949.BE

ABSTRACT

Objective To evaluate whether five days' treatment with injectable ampicillin plus gentamicin compared with chloramphenicol reduces treatment failure in children aged 2-59 months with community acquired very severe pneumonia in low resource settings.

Design Open label randomised controlled trial.

Setting Inpatient wards within tertiary care hospitals in Bangladesh, Ecuador, India, Mexico, Pakistan, Yemen, and Zambia.

Participants Children aged 2-59 months with WHO defined very severe pneumonia.

Intervention Chloramphenicol versus a combination of ampicillin plus gentamicin.

Main outcome measures Primary outcome measure was treatment failure at five days. Secondary outcomes were treatment failure defined similarly among all participants evaluated at 48 hours and at 10 and 21 days.

Results More children failed treatment with chloramphenicol at day 5 (16% v 11%; relative risk 1.43, 95% confidence interval 1.03 to 1.97) and also by days 10 and 21. Overall, 112 bacterial isolates were obtained from blood and lung aspirates in 110 children (11.5%), with the most common organisms being *Staphylococcus aureus* (n=47) and *Streptococcus pneumoniae* (n=22). In subgroup analysis, bacteraemia with any organism increased the risk of treatment failure at 21 days in the chloramphenicol group (2.09, 1.41 to 3.10) but not in the ampicillin plus gentamicin group (1.12, 0.59 to 2.13). Similarly, isolation of *S pneumoniae* increased the risk of treatment failure at day 21 (4.06, 2.73 to 6.03) and death (5.80, 2.62 to 12.85) in the chloramphenicol group but not in the ampicillin plus gentamicin group. No difference was found in treatment failure for children with *S aureus* bacteraemia in the two groups, but the power to detect a

difference in this subgroup analysis was low. Independent predictors of treatment failure by multivariate analysis were hypoxaemia (oxygen saturation <90%), receiving chloramphenicol, being female, and poor immunisation status.

Conclusion Injectable ampicillin plus gentamicin is superior to injectable chloramphenicol for the treatment of community acquired very severe pneumonia in children aged 2-59 months in low resource settings.

Trial registration Current Controlled Trials [ISRCTN39543942](http://www.clinicaltrials.gov/ct2/show/study?term=ISRCTN39543942).

INTRODUCTION

Pneumonia is a leading cause of death in under 5s in low resource settings.¹⁻³ Very severe pneumonia carries the highest mortality.⁴ First line treatment recommended by WHO is injectable chloramphenicol followed by oral chloramphenicol⁵ against the common bacterial pathogens: *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and Gram negative bacteria such as *Escherichia coli*.^{6,7}

The increasing resistance of bacteria, particularly *H influenzae* and *S aureus*, to chloramphenicol adds to the concerns that it is bacteriostatic and associated with bone marrow toxicity, particularly in malnourished children.⁸⁻¹³ An alternative regimen being used in some areas, ampicillin plus gentamicin, is bactericidal and provides good coverage against *H influenzae*, *S pneumoniae*, *E coli*, and *Proteus mirabilis*.

Given the lack of evidence on regimens other than chloramphenicol, we carried out a multicentre study to determine if injectable ampicillin plus gentamicin is superior to injectable chloramphenicol for the treatment of very severe pneumonia in children aged 2-59 months in seven developing countries.