Interventions for the interruption or reduction of the spread of respiratory viruses (Review)

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Interventions for the interruption or reduction of the spread of respiratory viruses

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A B S T R A C T

Background

Viral epidemics or pandemics such as of influenza or severe acute respiratory syndrome (SARS) pose a significant threat. Antiviral drugs and vaccination may not be adequate to prevent catastrophe in such an event.

Objectives

To systematically review the evidence of effectiveness of interventions to interrupt or reduce the spread of respiratory viruses (excluding vaccines and antiviral drugs, which have been previously reviewed).

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2006, issue 4); MEDLINE (1966 to November 2006); OLDMEDLINE (1950 to 1965); EMBASE (1990 to November 2006); and CINAHL (1982 to November 2006).

Selection criteria

We scanned 2300 titles, excluded 2162 and retrieved the full papers of 138 trials, including 49 papers of 51 studies. The quality of three randomised controlled trials (RCTs) was poor; as were most cluster RCTs. The observational studies were of mixed quality. We were only able to meta-analyse case-control data. We searched for any interventions to prevent viral transmission of respiratory viruses (isolation, quarantine, social distancing, barriers, personal protection and hygiene). Study design included RCTs, cohort studies, case-control studies, cross-over studies, before-after, and time series studies.

Data collection and analysis

We scanned the titles, abstracts and full text articles using a standardised form to assess eligibility. RCTs were assessed according to randomisation method, allocation generation, concealment, blinding, and follow up. Non-RCTs were assessed for the presence of potential confounders and classified as low, medium, and high risk of bias.

Main results

The highest quality cluster RCTs suggest respiratory virus spread can be prevented by hygienic measures around younger children. Additional benefit from reduced transmission from children to other household members is broadly supported in results of other study designs, where the potential for confounding is greater. The six case-control studies suggested that implementing barriers to transmission, isolation, and hygienic measures are effective at containing respiratory virus epidemics. We found limited evidence that the more uncomfortable and expensive N95 masks were superior to simple surgical masks. The incremental effect of adding virucidals or antiseptics to normal handwashing to decrease respiratory disease remains uncertain. The lack of proper evaluation of global measures such as screening at entry ports and social distancing prevent firm conclusions about these measures.

Authors' conclusions

Many simple and probably low-cost interventions would be useful for reducing the transmission of epidemic respiratory viruses. Routine long-term implementation of some of the measures assessed might be difficult without the threat of a looming epidemic.

PLAIN LANGUAGE SUMMARY

Interventions to interrupt or reduce the spread of respiratory viruses

Although respiratory viruses usually only cause minor disease, they can cause epidemics. Approximately 10% to 15% of people worldwide contract influenza annually, with attack rates as high as 50% during major epidemics. Global pandemic viral infections have been devastating because of their wide spread. In 2003 the severe acute respiratory syndrome (SARS) epidemic affected ~8,000 people, killed 780, and caused an enormous social and economic crisis. A new avian influenza pandemic caused by the H5N1 strain might be more catastrophic. Single measures (particularly the use of vaccines or antiviral drugs) may be insufficient to interrupt the spread.

We found 51 studies including randomised controlled trials (RCTs) and observational studies with a mixed risk of bias.

Respiratory virus spread might be prevented by hygienic measures around younger children. These might also reduce transmission from children to other household members. Implementing barriers to transmission, isolation, and hygienic measures may be effective at containing respiratory virus epidemics. There was limited evidence that (more uncomfortable and expensive) N95 masks were superior to simple ones. Adding virucidals or antiseptics to normal handwashing is of uncertain benefit. There is insufficient evaluation of global measures such as screening at entry ports and social distancing.

BACKGROUND

Description of the condition

There is increasing concern that a global pandemic viral infection may seriously affect humans. In 2002 to 2003 a novel severe acute respiratory syndrome (SARS) epidemic, caused by a coronavirus, swept the world. About 8000 people were affected and 780 (including a high number of healthcare workers) died. Overshadowing this calamity was an enormous social and economic crisis, especially in Asia (Shute 2003). There is now increasing concern about the threat of a new viral pandemic, arising from avian influenza, caused by the H5N1 strain (WHO 2004). Although most influenza cases recover fully, in the USA influenza causes approximately 36,000 deaths and 226,000 hospitalisations annually (USDHHS 2005). It is estimated that annually, approximately 10% to 15% of people globally contract influenza. During major epidemics, the attack rate of influenza may be as high as 50%. It is associated with increased general practice consultation rates, hospital admissions (Fleming 2000) and excess deaths (Fleming 2000; Simonsen 1997). It must also be considered in terms of increased days lost with absence from work and school, healthcare planning and influenza pandemic planning (Smith 2006).

High viral load and high viral infectiousness are likely to be the drivers of an influenza pandemic (Jefferson 2006a) and other serious epidemics such as with SARS. Other factors which contribute to influenza pandemics include an antigenic shift in the virus. An antigenic shift is a major change in the genetic makeup of the virus which creates a new subtype against which there is little circulating natural immunity (Smith 2006), as most people have not been exposed to this new virus and therefore are susceptible to infection. These pandemics were thought to originate in southern China, where ducks (the animal reservoir and breeding ground for new strains), pigs (which are thought to be the biological intermediate host or 'mixing vessel') and humans live in very close proximity (Bonn 1997). Pigs are considered plausible intermediate hosts as their respiratory epithelium cells have receptors for both avian (such as duck) and human viral hemagglutinins (Bonn 1997). Minor changes in viral antigenic configurations, known as 'drift', cause local or more circumscribed epidemics (Smith 2006).

Description of the intervention

There is increasing evidence (Jefferson 2005a; Jefferson 2005b; Jefferson 2005c; Jefferson 2006a) that single measures (such as the use of vaccines or antivirals) may be insufficient to interrupt the spread of influenza. However a recent trial showed that handwashing may be effective in diminishing mortality for respiratory disease (Luby 2005). The possible effectiveness of public health measures during the 'Spanish Flu' pandemic of 1918 to 1919 (Bootsma 2007) in US cities led us to wonder what evidence exists on the effectiveness of combined public health measures such as isolation, distancing and barriers. We also considered the major social implications for any community adopting them (CDC 2005a; CDC 2005b; WHO 2006). Given the potential global importance of interrupting viral transmission, up-to-date, concise estimates of effectiveness are necessary to inform planning and decision making. We could find no previous systematic review of such evidence.

OBJECTIVES

We systematically reviewed the evidence of effectiveness of interventions to interrupt or reduce the spread of respiratory viruses causing influenza-like illnesses (excluding vaccines and antivirals, which have already been covered in Cochrane reviews (Demicheli 2004; Jefferson 1999; Jefferson 2006b; Matheson 2003; Smith 2006; Swingler 2003)).

METHODS

Criteria for considering studies for this review

Types of studies

We considered trials (individual-level or cluster randomised, or quasi-randomised), observational studies (cohort and case-control designs), and any other comparative design, provided some attempt had been made to control for confounding, carried out in people of all ages.

Types of participants

People of all ages.

Types of interventions

We included any intervention to prevent viral animal-to-human or human-to-human transmission of respiratory viruses (isolation, quarantine, social distancing, barriers, personal protection and hygiene) compared with doing nothing or with another intervention. We excluded vaccines and antivirals.

Types of outcome measures

- Deaths;
- Numbers of cases of viral illness;
- Severity of viral illness in the compared populations. In children and healthy adults we measured burden by consequences of influenza, for example, losses in productivity due to absenteeism by parents. For the elderly in the community, we measured the burden by repeated primary healthcare contacts, hospital admissions, and the risk of complications;
- Any proxies for these.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2006, issue 4); MEDLINE (1966 to November 2006); OLDMEDLINE (1950 to 1965); EMBASE (1990 to November 2006); and CINAHL (1982 to November 2006). The MEDLINE search terms were modified for OLDMEDLINE, EMBASE and CINAHL.

MEDLINE (OVID)

1 exp Influenza, Human/
2 influenza.mp.
3 flu.mp.
4 exp Common Cold/
5 common cold.mp.
6 exp Rhinovirus/
7 rhinovirus$.mp.
8 exp Adenoviridae/
9 adenovirus$.mp.
10 exp Coronavirus/
11 exp Coronavirus Infections/
12 coronavirus$.mp.
13 exp Respiratory Syncytial Viruses/
14 exp Respiratory Syncytial Virus Infections/
15 respiratory syncytial virus$.mp.
16 respiratory syncythial virus$.mp.
17 exp Parainfluenza Virus 1, Human/
18 exp Parainfluenza Virus 2, Human/
19 exp Parainfluenza Virus 3, Human/
20 exp Parainfluenza Virus 4, Human/
21 (parainfluenza or para-influenza or para influenza).mp.
22 exp Severe Acute Respiratory Syndrome/
23 (severe acute respiratory syndrome or SARS).mp.
24 acute respiratory infection$.mp.
25 acute respiratory tract infection$.mp.
26 or/1-25
27 exp Handwashing/
28 (handwashing or hand washing or hand-washing).mp.
29 hand hygiene.mp.
30 (sanitizer$ or sanitiser$).mp.
31 (cleanser$ or disinfectant$).mp.
32 exp Gloves, Protective/
33 exp Gloves, Surgical/
34 glov$.mp.
35 exp Masks/
36 mask$.mp.
37 exp Patient Isolators/
38 exp Patient Isolation/
39 barrier$.mp.
40 curtain$.mp.
41 partition$.mp.

42 negative pressure room$.mp.
43 reverse barrier nursing.mp.
44 Cross Infection/pc [Prevention & Control]
45 school closure$.mp.
46 (clos$ adj3 school$).mp.
47 mass gathering$.mp.
48 public gathering$.mp.
49 (ban or bans or banned or banning).mp.
50 (outbreak$ adj3 control$).mp.
51 distancing.mp.
52 exp Quarantine/
53 quarantin$.mp.
54 or/27-53
55 26 and 54
56 Animals/
57 Humans/
58 56 not 57
59 55 not 58

Searching other resources

There were no language restrictions. Study-design filters included trials, cohort case-control and cross-over studies, and before-after and time series. We scanned the references of all included studies to identify other potentially relevant studies. We also accessed the archives of the former MRC Common Cold Unit (Jefferson 2005d) as a possible source for interruption of transmission evidence.

Data collection and analysis

Selection of studies

After conducting the searches we scanned the titles and abstracts. If a study appeared to meet our eligibility criteria (or when there was insufficient information to exclude it), we obtained full text articles. We then used a standardised form to assess the eligibility of each study based on the full article.

Data extraction and management

Two review authors (TOJ, CDM) independently applied inclusion criteria to all identified and retrieved articles. Four review authors (TOJ, EF, BH, AP) extracted data from included studies and checked their accuracy on standard Cochrane Vaccines Field forms. The procedure was supervised and arbitrated by CDM.

Aggregation of data was dependent on study design, types of comparisons, sensitivity and homogeneity of definitions of exposure, populations, and outcomes used. We calculated the statistic I^2 for each pooled estimate to assess the impact on statistical heterogeneity (Higgins 2002; Higgins 2003).

When possible, we performed a quantitative analysis and summarised effectiveness as odds ratio (OR) using 95% confidence intervals (CI). We expressed absolute intervention effectiveness as a percentage using the formula intervention effectiveness = 1 - OR, whenever significant. In studies which could not be pooled,

we used the effect measures reported by the trial authors (such as relative risk (RR) or incidence rate ratio (IRR) with 95% CI or, when these where not available, relevant P values).

No authors were contacted.

Assessment of risk of bias in included studies

We analysed randomised and non-randomised studies separately. Randomised studies were assessed according to: randomisation; generation of the allocation sequence; allocation concealment; blinding; and follow up. Non-randomised studies were assessed for the presence of potential confounders using the appropriate Newcastle-Ottawa Scales (NOS) (Wells 2005) for case-control and cohort studies; and a three-point checklist for controlled before and after and ecological studies (Khan 2000).

Using quality as a means of interpreting the results at the analysis stage, we assigned risk of bias categories on the basis of the number of items judged inadequate in each study: 1) low risk of bias, up to one inadequate item; 2) medium risk of bias, up to three inadequate items; and 3) high risk of bias, more than three inadequate items.

Subgroup analysis and investigation of heterogeneity

An a priori subgroup analysis was planned for:
1. pandemic influenza outbreaks;
2. seasonal influenza;
3. other epidemics (for example, SARS).

We had sufficient data to carry out only the last point.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

See 'Characteristics of included studies' table.

Risk of bias in included studies

The three RCTs were poorly reported with no description of randomisation sequence, concealment, or allocation (Gwaltney 1980; Turner 2004a; Turner 2004b). The design of two trials by one author means their results may not be generalised to everyday situations. This is due to the artefactual delivery of the interventions tested (see Quality issues in the Discussion section) (Turner 2004a; Turner 2004b).

The quality of the cluster randomised trials varied. Only the highest quality trials (Luby 2005; Roberts 2000; Sandora 2005) reported cluster coefficients and conducted analysis of data by unit of (cluster) allocation instead of by individuals. This common problem leads to spuriously narrow confidence intervals around the estimates of effect (Grimshaw 2004). Other common problems were a lack of description of randomisation procedure, partial

reporting of outcomes, unclear numerators or denominators and unexplained attrition (Carabin 1999; Kotch 1994; Morton 2004; White 2001), and either complete failure of double blinding (Farr 1988a; Farr 1988b) or inappropriate choice of placebo (Longini 1988).

We classified four of the six case-control studies as having medium risk of bias (Lau 2004a; Seto 2003; Wu 2004; Yin 2004) and two as at low risk of bias (Nishiura 2005; Teleman 2004), mostly because of inconsistencies in the text and lack of adequate description of controls.

Six of the 14 prospective cohort studies were classified as at low risk of bias (Agah 1987; Dick 1986; Falsey 1999; Leung 2004; Madge 1992; Somogyi 2004), four as of medium risk (Dyer 2000; Kimel 1996; Murphy 1981; White 2003), and three as of high risk of bias (Makris 2000; Master 1997; Niffenegger 1997). One was a very brief report of a small study with insufficient details to allow assessment (Derrick 2005).

All four retrospective cohort studies had high risk of bias (Doherty 1998; Isaacs 1991; Ou 2003; Yen 2006).

Six of the 13 controlled before-after studies were at low risk of bias (Hall 1981a; Leclair 1987; Macartney 2000; Pang 2003; Ryan 2001; Simon 2006), two of medium risk (Krasinski 1990; Pelke 1994) and five at high risk (Gala 1986; Hall 1981b; Heymann 2004; Krilov 1996; Snydman 1988).

The most common problem in all of these studies was a lack of reporting of viral circulation of the reference population, making interpretation and generalisability of their conclusions questionable.

Effects of interventions

We identified and screened 2300 titles of reports of potentially relevant studies; 2162 were excluded. We retrieved 138 full papers including 49 publications of 51 studies.

Reported results from randomised studies

Three studies tested the effects of cleaning hands on inactivating the virus and preventing experimental rhinovirus colds. These resulted in either a reduction in the incidence of rhinovirus infection among volunteers treated using different combinations of the acids used for cleaning (P = 0.025) (Turner 2004a) or did not reach statistical significance (13% versus 30% with combined denominator of only 60) (Turner 2004b). Using iodine treatment of fingers, 1 out of 10 volunteers were infected compared to 6 out of 10 in the placebo preparation arm (P = 0.06 with Fisher's exact test) (Gwaltney 1980).

Three cluster randomised studies tested the effects of virucidal cleaning disposable handkerchief wipes on the incidence and spread of acute respiratory infections (ARIs). One reported a reduced incidence of ARIs in the household over 26 weeks, from 14% to 5% (Farr 1988a). A similar study reported a small non-significant (5%) drop across families (Farr 1988b). However, since the drop in incidence was confined to primary illness, unaffected

by tissue use, we might assume they were ineffective. A community trial also reported a non-significant reduction in ARI secondary attack rates (18.7% versus 11.8%) during a time of high circulation of influenza H3N2 and rhinoviruses in the community (Longini 1988). This result is likely to be an underestimate because of any barrier effect of the inert tissue wipes used in controls.

Seven cluster randomised studies tested educational programmes to promote handwashing, with or without the adjunct of antiseptic agents, on the incidence of ARIs either in schools or in households. Because of different definitions, comparisons, lack of reporting of cluster coefficients, and (in two cases) missing participant data (Carabin 1999; Kotch 1994), we judged it improper to meta-analyse the data. Two of these trials reported a lack of effect: RR for the prevention of acute respiratory illness of 0.94 (95% CI -2.43 to 0.66) (Kotch 1994); and 0.97 (95% CI 0.72 to 1.30) (Sandora 2005). Nevertheless, the highest quality trials reported a significant decrease in respiratory illness in children up to 24 months (RR 0.90, 95% CI 0.83 to 0.97), although the decrease was not significant in older children (RR 0.95, 95% CI 0.89 to 1.01) (Roberts 2000); and a 50% (95% CI - 65% to -34%) lower incidence of pneumonia in children aged less than five years of age in a developing country (Luby 2005). Another study reported a decrease of 30% to 38% in respiratory infections with additional hand-rubbing (RR for illness absence incidence 0.69, RR for absence duration 0.71) (White 2001). One study reported decreased school absenteeism of 43% with the additional use of alcohol gel as well as handwashing (Morton 2004). Two trials reported that repeated handwashing significantly reduced the incidence of colds by as much as 20% (Carabin 1999; Ladegaard 1999).

Reported results from case-control studies

Six case-control studies assessed the impact of public health measures to curb the spread of the SARS epidemic during February to June 2003 in China, Singapore, and Vietnam. Homogeneity of case definition, agent, settings, and outcomes allowed meta-analysis. Binary data were pooled; none of the comparisons showed significant heterogeneity, so we used a fixed-effect model. Although continuous data were often available, the variables were different and measured in different units with standard deviations usually missing, which prevented their meta-analysis.

Studies reported that disinfection of living quarters was highly effective in preventing the spread of SARS (OR 0.30, 95% CI 0.23 to 0.39) (Lau 2004a); handwashing for a minimum of 11 times daily prevented most cases (OR 0.45, 95% CI 0.36 to 0.57), based on all six studies (Lau 2004a; Nishiura 2005; Seto 2003; Teleman 2004; Wu 2004; Yin 2004); simple mask wearing was highly effective (OR 0.32, 95% CI 0.25 to 0.40), based on five studies (Lau 2004a; Nishiura 2005; Seto 2003; Wu 2004; Yin 2004); two studies found N95 mask wearing even more effective (OR 0.09, 95% CI 0.03 to 0.30) (Seto 2003; Teleman 2004); glove wearing was effective (OR 0.43, 95% CI 0.29 to 0.65) (Nishiura 2005; Seto 2003; Teleman 2004; Yin 2004); gown wearing was also effective (OR 0.23, 95% CI .14 to 0.37) (Nishiura 2005; Seto 2003;

Teleman 2004; Yin 2004); and all means combined (handwashing, masks, gloves, and gowns) achieved very high effectiveness (OR 0.09, 95% CI 0.02 to 0.35) (Nishiura 2005; Seto 2003). All studies selected cases from hospitals, except for one (Lau 2004a) in which cases were people with probable SARS reported to the Department of Health in Hong Kong.

Prospective cohort studies

Using an alcohol rub in students' communal residences resulted in significantly fewer symptoms (reductions of 14.8% to 39.9 %) and lower absenteeism (40% reduction) (White 2003). In a much-cited small experimental study, virucidal paper handkerchiefs containing citric acid interrupted the transmission of rhinovirus colds transmitted through playing cards: 42% of re-usable cotton handkerchief users developed colds compared with none using disposable virucidal tissues (Dick 1986).

Few identified studies reported interventions in the day-care setting, either in staff or patients. Perhaps more than the additional portable virucidal hand foam as an adjunct to handwashing, one staff educational programme on handwashing in a day-care centre for adults was effective over the last four years in reducing rates of respiratory infection in day-care patients from 14.5 to 10.4 per 100 person-months to 5.7 (P < 0.001), with an accompanying decline in viral isolates (Falsey 1999). This confirmed an earlier report of the effectiveness of a handwashing programme in reducing absenteeism for influenza-like illness in a primary school (Kimel 1996).

Two high risk of bias studies reported that education, a handwashing routine, and encouragement for kindergarten children, parents and staff in correct sneezing and coughing procedure were effective, although there were considerable fluctuations in incidence of infections in the control and test centres (Niffenegger 1997); but were not effective in reducing absenteeism caused by acute respiratory infections (RR 0.79, P = 0.756) (Master 1997).

Dyer and colleagues reported a prospective cluster open-label cross-over cohort study. The study assessed the effectiveness of a hand sanitiser in conjunction with at will soap-and-water handwashing in a private elementary school in California. Use of the sanitiser reduced illness absenteeism by 41.9% (reduction in respiratory illnesses of 49.7% over the 10-week period of the study) (Dyer 2000).

Curiously, an infection-control education programme reinforcing handwashing and other hygienic measures in a nosocomial setting reported reducing the number of organisms present on hands and surfaces, and acute respiratory infections, although the data tabled suggested the opposite (an incidence rate of 4.15/1000 patient-days in the test homes versus 3.15/1000 in the control homes) (Makris 2000).

A study found wearing a goggle-mask apparatus in healthcare workers visiting and caring for children aged up to five with respiratory syncytial virus (RSV) and symptoms of respiratory disease was effective (5% illness rate in goggle wearers against 61% in no-goggle controls) (Agah 1987).

Rapid laboratory diagnosis, cohort nursing, and the wearing of gowns and gloves for all contacts with RSV-infected children significantly reduced the risk of nosocomial RSV infection (OR 0.013 to 0.76) (Madge 1992), although another similar study reported no effect of adding the use of both gown and mask to the usual handwashing routine on the development of illness in personnel caring for infants with respiratory disease (4 out of 30 in the handwashing group alone compared to 5 out of 28 in the handwashing, gown, and masking group, P > 0.20); although the authors described poor compliance with the barrier protocol (Murphy 1981). Strict procedures of triage and infection control to stop transmission of SARS from infected children to carers and visitors of a large hospital at the height of the epidemic in 2003 in Hong Kong was reported effective at interruption of transmission as no healthcare worker became ill, in contrast to experiences in other institutions (Leung 2004).

A tiny study comparing the N95 mask with paper surgical masks in volunteers found that surgical masks, even when worn in multiple layers (up to five), filtered ambient particles poorly (Derrick 2005); this principle was confirmed in another small study of air filtration to prevent droplet spread (Somogyi 2004).

Retrospective cohort studies

Two studies investigated isolating together children less than three years of age with suspected RSV. In one, transmission was diminished by "up to 60%" (Isaacs 1991), while the statement that nosocomial transmission "was minimised" was not supported by data in the other study (Doherty 1998).

Isolation of cases during the 2003 epidemic of SARS in China was reported to limit transmission only to those contacts who actually had home or hospital contact with a symptomatic SARS patient (attack rate 31.1%, 95% CI 20.2 to 44.4 for carers; 8.9%, 95% CI 2.9 to 22.1 for visitors; 4.6%, 95% CI 2.3 to 8.9 for those living with a SARS case) but not to contacts living in the same building, working with cases, or without contact with SARS cases during the incubation period. This suggests extending quarantine only for contacts of symptomatic SARS cases (Ou 2003).

Another brief report carried out in 2003 during the SARS epidemic, in a military hospital in Taiwan, China and 86 control hospitals, compared an integrated infection-control policy to protect healthcare workers against infection; only two from the military hospital were infected with SARS compared to 43 suspected and 50 probable cases in the control hospitals (Yen 2006).

Controlled before-and-after studies

Two small studies by the same first author assessed means of nosocomial transmission of RSV in small children and the effects of introducing distancing and barriers: one with low risk of bias reported effective physical distancing and room separation (0 infected out of 14 who sat away from RSV-infected infants compared with 5 out of 7 who cuddled and 4 out of 10 who touched infected infants) (Hall 1981a). The second with high risk of bias reported no incremental benefits of gowns and masks (32% infec-

tion versus 41%) (Hall 1981b). Adding disposable plastic eye-nose goggles to other respiratory infection-control procedures (isolating infected from uninfected people, handwashing) also reduced transmission of RSV (6% versus 42% of controls) (Gala 1986). Screening and subsequent isolation of infected from uninfected people ('cohorting') also reduced nosocomial RSV transmission in older children (from 5.33 infections per 1000/patient days of care to 1.23 infections per 1000/patient days after introduction of screening) (Krasinski 1990). A similar study reported that increased compliance with a policy of glove and gown isolation precautions reduced the high rate of nosocomial RSV transmission on an infant and toddler ward (RR for pre- and post-intervention periods infection rates 2.9, 95% CI 1.5 to 5.7) (Leclair 1987).

A study of protective gowning did not protect neonatal intensive care unit infants from RSV or any other type of infection, or affect mortality (1.21 per 100 patient-days of gowning compared to 1.38 of none), although selection bias was likely with 17% of participating children lost to follow up (Pelke 1994).

A German study conducted over three seasons reported a huge decrease of nosocomial RSV infections, from 1.67/1000 patient-days in the first season to 0.18/1000 patient-days in the last season, after instituting enhanced surveillance and feedback, rapid diagnosis, barriers and isolation, and disinfection of surfaces (Simon 2006). A similar study but with high risk of bias reported a decrease from eight confirmed RSV cases per 1000 patient days to none (Snydman 1988). A better conducted study over eight years implemented a combination of education with high index of suspicion for case-finding (contact precautions), with barriers (but no goggles or masks) and handwashing for patients and staff reduced RSV infections in a hospital in Philadelphia (USA): RR 0.61, 95% CI 0.53 to 0.69 (Macartney 2000).

One small study with serious potential biases assessed training and a sanitary programme (handwashing, disinfection of school buses, appliances and toys) in a special-needs day-care facility for Downs children, a pupil to staff ratio of 5 or 6 to 1, and reported reductions in: respiratory illnesses from a mean of 0.67 to 0.42 per child per month (P < 0.07); physician visits from 0.50 to 0.33 (P < 0.05); mean courses of antibiotics prescribed from 0.33 to 0.28 (P < 0.05); and days of school missed because of respiratory infections from 0.75 to 0.40 (P < 0.05) (Krilov 1996).

A very large study of military recruits reported that a structured top-down programme of handwashing at least five times daily nearly halved the incidence of acute respiratory infections. Recruits who handwashed less frequently reported more episodes of acute respiratory tract infections (OR 1.5, 95% CI 1.2 to 1.8), which represents a difference of 4.7 versus 3.2 mean infections per recruit per year, and more hospitalisations (OR 10.9, 95% CI 2.7 to 46.2). However, implementation was difficult (Ryan 2001).

An ecological study analysed the effects of quarantine and port of entry screening on the SARS epidemic in early 2003 in Beijing, China, from data collected centrally. Hospitals were the initial sources of transmission of the SARS virus. The shape of the

epidemic suggests these measures may have reduced SARS transmission although only 12 cases identified out of over 13 million people screened puts in doubt the direct effectiveness of entry port checks at airports and railway stations, and screening was probably more important (Pang 2003).

An Israeli study of 186,094 children aged 6 to 12 years reported that school closure was temporally associated with a 42% decreased morbidity from respiratory tract infections, a consequent 28% decrease in visits to physicians and to emergency departments, and a 35% reduction in purchase of medications (Heymann 2004).

D I S C U S S I O N

Quality issues

Several features need consideration before drawing generalisations from these studies.

The settings of the studies, conducted over four decades, were heterogeneous and ranged from suburban schools (Carabin 1999; Dyer 2000; Heymann 2004; Niffenegger 1997) to military barracks (Ryan 2001), intensive care units, and paediatric wards (Gala 1986; Leclair 1987) in industrialised countries; slums in low-income countries (Luby 2005); and special-needs day-care centres with a very high teacher to pupil ratio (Krilov 1996). Few attempts were made to obtain socio-economic diversity by (for example) involving more schools in the evaluations of the same programme (Dyer 2000). We were able to identify few studies from low-income countries where the vast majority of the burden lies, and where cheap interventions are so critical. Even in Western countries, such as Israel, the dramatic fall in acute respiratory infections (ARIs) subsequent to school closure may have been related to that country's high child population (34%). Additionally, limited availability of over-the-counter medications and national universal comprehensive health insurance provided with consequent physician prescription of symptomatic treatment may limit generalisability of findings further (Heymann 2004).

The variable quality of the methods of these studies is striking. Hasty design of interventions for public health crises, particularly the six case-control studies, is understandable but less so when no randomisation - not even of clusters - was carried out in several unhurried cohort and before-and-after studies. Randomisation could often have involved minimal disruption to service delivery. Inadequate reporting especially made interpretation difficult of before-after studies. Incomplete or no reporting of: randomisation (Turner 2004a); blinding (Farr 1988a; Farr 1988b); numerators and denominators (Carabin 1999; Kotch 1994); interventions; outcomes (White 2003); participant attrition (Makris 2000); confidence intervals (Madge 1992); and cluster coefficients in the relevant trials (Carabin 1999) led to a considerable loss of information. Potential biases (such as cash incentives given to participants (White 2003)) were not discussed. Some authors even

confused cohort with before-after designs to elaborate conclusions unsupported by their data (Makris 2000). Methodological quality was sometimes eroded by the need to deliver behavioural interventions in the midst of service delivery (Niffenegger 1997).

Nonetheless, even when suboptimal designs were selected, trial authors rarely attempted to articulate potential confounders. A commonly ignored confounder, specific to this area, is the huge variability in viral incidence (Heymann 2004; Isaacs 1991). Sometimes this was addressed in the study design (Falsey 1999), even in controlled before-and-after studies (one attempted correlation between RSV admissions and RSV circulating in the community) (Krasinski 1990). Another attempted linking exposure (measured as nasal excretion) and infection rate in the pre- and post-intervention periods (Leclair 1987).

Inappropriate placebos caused design problems. In some studies the placebo probably carried sufficient intervention effect to apparently dilute the intervention effects (Longini 1988). Two valiant attempts probably failed because placebo handkerchiefs were impregnated with a dummy compound which stung the users' nostrils (Farr 1988a; Farr 1988b).

Some studies used impractical interventions. Volunteers subjected to the intervention hand cleaner (organic acids) were not allowed to use their hands between cleaning and virus challenge, so the effect of normal use of the hands on the intervention remains unknown (Turner 2004a; Turner 2004b). Two per cent aqueous iodine painted on the hands, although a successful antiviral intervention, causes unacceptable cosmetic staining, impractical for all but those at the highest risk of epidemic contagion (Gwaltney 1980).

Compliance with interventions, especially educational programmes, was a problem for several studies despite the importance of many such low-cost interventions.

The evidence

The highest quality cluster randomised trials indicate most effect on preventing respiratory virus spread from hygienic measures in younger children. Perhaps this is because younger children are least capable of hygienic behaviour themselves (Roberts 2000), and have longer-lived infections and greater social contact, thereby acting as portals of infection into the household (Monto 1969). Additional benefit from reduced transmission from them to other members of the household is broadly supported from the results of other study designs where the potential for confounding is greater.

The six case-control studies suggest that implementing barriers to transmission, isolation, and hygienic measures are effective with the use of relatively cheap interventions to contain epidemics of respiratory viruses. We found limited evidence of the superior effectiveness of droplet barrier devices such as the N95 masks over simple surgical masks. N95 masks are respirators with 95% filtration capability against non-oily particulate aerosols (Teleman

2004). More expensive and uncomfortable (especially if worn for long periods) than simple surgical masks, they may be useful in very high risk situations.

It is uncertain whether the incremental effect of adding virucidals or antiseptics to normal handwashing actually decreased the respiratory disease burden outside the confines of the rather atypical studies, upon which we reported. The extra benefit may have been, at least in part, accrued by confounding additional routines.

Studies preventing transmission of RSV and similar viruses appeared to be closer to real life and suggest good effectiveness. However, methodological quality concerns of the controlled before-and-after studies, mentioned previously, suggest benefits may have been due to population differences, especially virus infection rates. These were poorly reported in most studies.

Routine long-term implementation of some of the measures assessed in this review would be problematic, particularly maintaining strict hygiene and barrier routines for long periods of time. This would probably only be feasible in highly motivated environments, such as hospitals, without a real threat of a looming epidemic. Most of the study authors commented on the major logistic burden that barrier routines imposed at the community level. However, the threat of a looming epidemic may provide stimulus for their inception.

A disappointing finding was the lack of proper evaluation of global and highly resource-intensive measures such as screening at entry ports and social distancing. The handful of studies (mostly conducted during the SARS epidemic) do not allow us to reach any firm conclusions.

AUTHORS' CONCLUSIONS

Implications for practice

The following effective interventions should be implemented, preferably in a combined fashion, to diminish transmission of viral respiratory disease:

- frequent handwashing with or without adjunct antiseptics;

- barrier measures such as gloves, gowns, and masks with filtration apparatus; and

- suspicion diagnosis with isolation of likely cases.

Most effort should be concentrated on reducing transmission from young children.

Implications for research

Public health measures can be highly effective, especially when they are part of a structured programme that includes instruction and education and when they are delivered together. There is a clear requirement to carry out further large pragmatic trials to evaluate the best combinations. Randomised controlled trials with a pragmatic design, similar to the Luby et al trial, should be carried out whenever possible (Luby 2005). Nevertheless, this systematic review of the available research does provide some important insights. Perhaps the impressive effect of the hygienic measures aimed at younger children derives from the children's poor capability with their own hygiene. The variable quality and small scale of some studies is known from descriptive studies (Aiello 2002; Fung 2006; WHO 2006) and systematic reviews of selected interventions (Meadows 2004).

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Agah 1987

Methods	Prospective cohort study carried out in California hospital during the autumn 1984 to spring 1985 season. The study assessed the efficacy of HCWs wearing goggle-mask apparatus while visiting and caring for children aged up to 5 with RSV and symptoms of respiratory disease compared to do-nothing. Children admitted with a RSV diagnosis were assigned to the 2 arms balanced for age and sex
Participants	168 healthcare workers (HCW) caring for children < 5 years with differential diagnosis of RSV
Interventions	Mask and goggles (sometimes gowns too) versus normal care
Outcomes	RSV illness reduced from 61% (controls) to 5% (intervention) Laboratory: swabs for RSV diagnosis Effectiveness: RSV illness Safety: N/A
Notes	Risk of bias: low Notes: The authors conclude that wearing mask and goggles significantly reduced transmission to HCWs and other children of RSV (61% versus 5% illness rate). Analysis is also given by number of contacts (data not extracted). A reasonably reported if difficult to conduct study. Standard procedures such as handwashing should not have acted as a confounder given 100% coverage among HCWs

Carabin 1999

Methods	Cluster randomised controlled trial carried out in day care centres (DCC) in the Canadian province of Quebec between 1 Sept 1996 and 30 November 1997 (15 months). The aim was to test the effects of a hygiene programme on the incidence of diarrhoea and fecal contamination (data not extracted) and on colds and URTIs. The design included before and after periods analysed to assess the Hawthorne effect of study participation on control DCCs. Unit of randomisation was DCC but analysis was also carried out at classroom and single child level. This is a common mistake in C-RCT analysis. DCCS were stratified by URTI incidence preceding the trial and randomised by location. Cluster coefficients are not reported
Participants	1729 children aged 18 to 36 months in 47 DCCs (83 toddler classrooms). Originally 52 eligible DCCs with 89 classrooms agreed to take part but 5 dropped out (2 closed, 1 was sold, 2 either did not provide data or the data were "unreliable" and 6 classrooms had insufficient data). Forty three children failing to attend DCC for at least 5 days in the autumn were also excluded. ITT analysis was carried out including an additional DCC whose director refused to let staff attend the training session
Interventions	Training session (1 day) with washing of hands, toy cleaning, window opening, sand pit cleaning and repeated exhortations to hand wash
Outcomes	Laboratory: N/A Effectiveness: diarrhoea and coliform contamination (data not extracted) Colds (nasal discharge with at least one of the following: fever, sneezing, cough, sore throat, earache, malaise, irritability)

Carabin 1999   (*Continued*)

	URTI (cold of at least 2 days' duration) Surveillance was carried out by educators, annotating absences or illness on calendars. Researchers also filled in a phone questionnaire with answers by DCC directors Safety: N/A
Notes	Risk of bias: high (no description of randomization; partial reporting of outcomes, numerators and denominators) Notes: the authors conclude that the intervention reduced the incidence of colds (IRR 0.80, 95% CI 0.68 to 0.93). Confusingly written study with unclear interweaving of two study designs. For unclear reasons analysis was only carried out for the first autumn. Unclear why colds are not reported in the results. Cluster coefficients and randomisation process not described

Derrick 2005

Methods	Prospective cohort study testing the performance of 1, 2, 3, 4 and 5 surgical masks worn in layers against the droplet filtration capacity of a N95 respirator. The study is described as cross-over trial when all volunteers wore the combinations of layers, but this is not further described
Participants	Six volunteers who wore the masks and had their droplet count taken
Interventions	Pleated rectangular three-ply surgical mask
Outcomes	Laboratory
Notes	Risk of bias: high (report too brief to allow assessment) Notes: The authors conclude that the best combination of five surgical masks scored a fit factor of 13.7, well below the minimum level of 100 required for a half face respirator. The reduction in particle count went from 2.7 for a singe mask to 5.5 for 5 masks worn at the same time. Multiple surgical masks filter ambient particles poorly. They should not be used as a substitute for N95 masks unless there is no alternative. Cautiously the authors state that they cannot comment on the capacity of five layers of masks to stop infections such as SARS as the infective count of the SARS-CoV is unknown. Fascinating small study with no details of assignment so it was classified as a cohort study. Unfortunately there is no indication of how comfortable 5 masks are to wear in a layer and no description of the volunteers

Dick 1986

Methods	Prospective cohort study involving men ~ 18 years of age. The objective of the study was to determine whether rhinovirus 16 colds could be stopped from spreading with the use of an highly virucidal paper handkerchief (CMF tissues) containing citric acid and other virucidal ingredients. Twenty to 25 men ~ 18 years of age were inoculated intranasally with a safety tested R16. The laboratory-induced cold was in all aspects comparable to natural colds. Eight of them with the most severe colds (donors) played cards with 12 antibody-free men (recipients) in a experiment room. Four experiments were conducted, in experiments B and C volunteers used CMS tissues to prevent spreading of R16 colds. In the two control experiments (A and D) volunteers were permitted to use cotton handkerchiefs
Participants	Males ~ 18 years of age with a laboratory-induced R 16 cold (donors) and 12 antibody-free men (recipients)
Interventions	Use of virucidal paper handkerchief (CMF tissues), containing citric acid and other virucidal ingredients to stop the spreading of R16 colds versus normal cotton handkerchiefs

Dick 1986 (*Continued*)

Outcomes	Laboratory: serological evidence (serum samples or viral isolation) Effectiveness: rhinovirus colds Safety: N/A
Notes	Risk of bias: low Notes: The authors concluded that the use of CMS tissues has been successful, because it determined a complete interruption of transmission of R16 among participants, stopping the spreading in an environment in which possibilities for transfer of virus were constant, and in which the rate of transmission was predictably high under standard conditions (42% of cotton handkerchief users developed colds, but no user of virucidal tissues did so)

Doherty 1998

Methods	Retrospective cohort study carried out in North Staffordshire hospital (UK) during two periods: from 1 November 1994 to 31 January 1995 and from 1 November 1995 to 31 January 1996. The study assessed the use at admission of assigning children to a cohort once a rapid enzyme immunoassay or immunofluorescence testing had identified RSV positive patients. The incidence of RSV illness was compared in cohorted and uncohorted children. The authors believed that this procedure would aid clinical management and minimize cross-infection from affected to susceptible patients. Nasopharyngeal aspirates were obtained from infants and young children with an acute respiratory illness. Aspirates were sent for rapid diagnostic testing. RSV positive patients were cohorted into six bedded bays on the paediatric ward. All carers observed standard routines (handwashing and gown wearing)
Participants	Children less than three years of age with an acute respiratory illness on admission. During the study periods a total of 222 patients in 1994 to 1995 and 291 patients in 1995 to 1996 had positive rapid tests
Interventions	RSV diagnosis and cohorting versus normal care
Outcomes	Laboratory: aspirates for RSV diagnosis Effectiveness: RSV illness (developed at least five days since admission) Safety: N/A "RSV infection reduced" (but data tabled do not support this conclusion)
Notes	Risk of bias: high (poor descriptions) Notes: the authors conclude that cohorting has been shown to reduce nosocomial transmission of RSV infections (no OR or other measures of strength are reported: "nosocomial transmission was minimised"). The study presents many inconsistencies between text and table and data were not extracted. The objective of the study is not well defined. Part of the results is in the discussion. Most of all it is unclear who the intervention and controls arms were (.i.e. cohorting of RSV infected children to prevent infection in whom?)

Dyer 2000

Methods	Prospective cluster open-label cross-over cohort study of programmed use of a hand sanitizer in conjunction with at-will soap-and-water hand washing conducted in a private elementary school in California. The aim of the study was to assess the effectiveness of the SAB sanitizer at reducing illness absenteeism in a school setting. Subjects were grouped by classroom without formal randomisation. Seven classes received the instant sanitizer, while the remaining seven classes were assigned to the control group. Male-to-female ratios and age distributions of the two groups did not differ significantly.

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Dyer 2000 (*Continued*)

Prior to study commencement all students participated in an educational program about germs and the importance of hand washing to prevent illnesses. Children in the hand sanitizer group received a spray to use under teacher supervision to supplement normal, at-will hand washing with soap and water. The control group was instructed to wash hands with water and soap, and it was not supervised. Data were collected for 10 weeks. After this period, there was a 2-week wash out period, during which neither group of students used SAB sanitiser. Then SAB sanitizer was distributed to the student group that had previously served as the control and the study proceeded for another 4 weeks

Participants	420 children in a private elementary school in California aged 5 to 12 years; cluster open-label crossover cohort study over 10 weeks
Interventions	Educational programme plus the SAB (surfactant, allontoin and benzal konium chloride) spray hand sanitizer in 1oz bottles fitted with a pump spray top and with at-will soap-and-water hand washing versus nothing
Outcomes	Laboratory: serological evidence: N/A Effectiveness: days of absences from school for respiratory illness (and gastrointestinal illness - data not extracted) Safety: N/A Respiratory illness and gastrointestinal illness: reduced absenteeism by 41.9%; respiratory illnesses by 49.7%
Notes	Risk of bias: medium Notes: The authors conclude that daily use of the SAB instant hand sanitizer with at-will hand washing using soap and water significantly decreased absences due to acute communicable illness. Use of the sanitizer reduced illness absenteeism by 41.9% (reduction in respiratory illnesses of 49.7% over the 10 week period of the study). The authors also described some limitations of the study, as limited socio-economic diversity in the study population, limitation to a single study site and lack of blinding. Further soap-and-water washing was not monitored. Generalisability of the results is questionable as all participants underwent the educational programme

Falsey 1999

Methods	Prospective cohort study conducted at three adult day-care centers in Rochester, New York. The study assessed the value of a staff educational program combined with the use of a portable virucidal hand foam for the reduction of respiratory infections in day-care participants. The authors report in the same paper an ecological study of the incidence of ILI in 3 previous seasons (1992 to 1996) which does not report numerators and denominators and was not extracted
Participants	In December 1995 when the study started there were center 1: 69 elderly and 36 staff members; center 2: 67 elderly and 45 staff members; center 3: 68 elderly and 16 staff members
Interventions	Addition of virucidal hand foam as a supplement versus normal handwashing and educational programme
Outcomes	Laboratory: serological evidence and virology cultures (Table 1 reports a series of isolated pathogens, with no tie in with actual cases) Effectiveness: viral pathogens: influenza A/B, RSV, coronavirus, parainfluenza, rhinovirus Safety: N/A
Notes	Risk of bias: low Notes: The authors conclude that the educational program for staff was associated with an almost 50% decrease in the infection rate in day-care attendees. The programme was effective only in the last of the four years of the programme (rates of infection in day-care patients fell from 14.5 to 10.4 per 100 person-months to 5.7 per 100 person months, P < 0.001). This is a conclusion based on an ecological study of the incidence of ILI in 3 previous seasons which the authors report in the same paper, but which does not report numerators and denominators and was not extracted. The lower infection rate is likely to reflect the combination of interventions and education, which increased staff

Falsey 1999 (*Continued*)

awareness and more broadly changed behaviour. There was no apparent additional benefit from the virucidal foam. This is one of the few identified studies reporting circulating viruses in the day-care setting, both in staff and patients. The decline in influenza-like illness episodes across the four study years is reflected in the decline in viral isolates, suggesting that aspecific measures such as handwashing are effective against the main respiratory viruses

Farr 1988a

Methods	The study was a six-month cluster randomised controlled double blind trial of the efficacy of virucidal nasal tissues in the prevention of natural cold, and it was conducted in Charlottesville, Virginia, USA. Many of the families were enrolled, because one or more members worked at the State Farm Insurance Company; the remaining families were recruited from the Charlottesville community by advertisement in a local newspaper. Families were randomly assigned by the sponsoring company to receive boxes of treated tissues, placebo tissues, or no tissues. The randomisation was performed by computer. Study participants and investigators were unaware of the type of tissues which each family was randomised to receive. Blinding efficacy was tested using a questionnaire: the mothers in each family were asked twice if she believed her family was using virucidal or placebo tissues. Participants in the treated and placebo groups were instructed to use only tissues received through the study, while families in the additional control group without tissues were allowed to continue their usual practice of personal hygiene. Each family member kept a daily listing of respiratory symptoms on a record card. A nurse epidemiologist visited each family monthly to encourage recording
Participants	186 families, 58 in the active group, 59 in the placebo group and 69 in the no tissues group. A total of 302 families were originally recruited, 116 families who did not comply with the study protocol, lost their surveillance cards, could not complete the protocol were excluded from the analysis
Interventions	Use of virucidal tissues versus placebo tissues versus no tissues. The treated tissues were impregnated with malic and citric acids and sodium lauryl sulfate, while placebo tissues contained saccharin
Outcomes	Laboratory: serological evidence: no Effectiveness: respiratory illness Safety: N/A
Notes	Risk of bias: high (failure of blinding) Notes: the authors conclude that virucidal tissues have only a small impact upon the overall rate of natural acute respiratory illnesses. The total illness rate was lower in families using virucidal tissues than in both of the other two study group, but only the difference between active and placebo groups was statistically significant (3.4 illness per person versus 3.9 for placebo group, P = 0.04 and 3.6 for no tissues control group P = 0.2, and overall 14% to 5% reduction). The questionnaire results suggest that some bias may have been present since a majority of mothers in the virucide group believed they were receiving the "active" tissues. Another possible explanation of the low effectiveness of virucidal tissues is poor compliance by children in the use of virucidal tissues. A well designed and honestly reported study

Farr 1988b

Methods	The study was a six-month randomised controlled double blind trial of the efficacy of virucidal nasal tissues in the prevention of natural cold, and it was conducted in Charlottesville, Virginia. Families were recruited from the Charlottesville community by advertisement in a local newspaper. Families were randomly assigned by the sponsoring

Farr 1988b (*Continued*)

company to receive either virucidal tissues, or placebo-treated tissues. Stratified randomisation was performed by computer and the strata were defined by total number in the family. Study participants and investigators were unaware of the type of tissues which each family was randomised to receive. Each family member kept a daily listing of respiratory symptoms on a record card. A nurse epidemiologist visited each family monthly to encourage recording. In addition a study monitor visited each family bimonthly to further encourage compliance and reporting of symptoms

Participants	98 families, 58 in the active group and 40 in the placebo group. Two-hundred and thirty-one families were initially recruited, 222 completed the trial, data of 98 families were analysed. The others were excluded from the analysis since they complained of side effects (sneezing etc) or reported not using the tissues regularly
Interventions	Use of virucidal tissues versus placebo tissues. The treated tissues were impregnated with malic and citric acids and sodium lauryl sulfate, while placebo tissues contained succinin acid. Participants in the treated and placebo groups were instructed to use only tissues received through the study
Outcomes	Laboratory: serological evidence: no Effectiveness: respiratory illness Safety: N/A
Notes	Risk of bias: high (failure of blinding) Notes: the study suggests that virucidal tissues have only a small impact upon the overall rate of natural acute respiratory illnesses. The total illness rate was lower in families using virucidal tissues than in the other study group, but the difference between active and placebo groups was not statistically significant. There was a small non significant drop in illness rates across families (5%). The tissues appeared ineffective as the drop was confined to primary illness unaffected by tissue use. Placebo (succinin acid) was not inert, and it was associated with cough and nasal burning. This impacted on allocation concealment. A well designed and honestly reported study marred by transparent allocation

Gala 1986

Methods	The purpose of this study was to evaluate whether the use of a disposable plastic goggle designed to cover the eyes and nose could help reduce the rate of nosocomial infections during an outbreak of RSV infection. The rates of RSV infection in staff members and infants were determined on an infant and toddler ward during a seven-week. Two 3 week study periods were compared: period 1, during which all staff members used the goggles, and period 2, were no goggles were worn. The respiratory infection control procedures were the same during both periods of study: hand washing, isolation and cohorting. In reality although on report, Gala and colleagues are conducting two studies. The first is a non-concurrent cohort study, in which two different population of children are assessed separated by a 1 week "washout" period and the intervention (goggles) on staff. The play of confounders here is too heavy and uncontrolled to include the data in the study. The second is a controlled before and after on the 40-odd members of staff (32 of whom took part in both periods). Here the play of confounders should be partly reduced. We extracted data relating to the second study only
Participants	74 Children and 40 staff members in period 177 children and 41 staff members in period 2. During the study 151 children were admitted to the ward; their mean age was 12.9 months, 59% were boys. During period 174 infants were examined, 15 were admitted with RSV infections, the remaining 59 constituted the group potentially susceptible to a nosocomial RSV infection. Seventeen infants were hospitalised for sufficient time for a nosocomial infection and in one nosocomial RSV infection was detected. During period 277 babies were studied, 17 of whom were admitted with RSV infection. Of the remaining 60, 39 children were excluded, 21 were considered susceptible, and in 9 of them nosocomial RSV infection was detected. Forty staff members were examined in period 1 and 41 during period 2. During period 2, two of the ward staff were acquired RSV infection and were not considered susceptible

Gala 1986 (*Continued*)

Interventions	Use of a disposable plastic eye-nose goggle and respiratory infection control procedures vs. only respiratory infection
Outcomes	Laboratory: serological evidence Effectiveness: RSV infection (symptoms and laboratory confirmation) Safety: N/A
Notes	Risk of bias: high Notes: The use of the disposable eye-nose goggles appeared to be associated with a significant decrease in nosocomial RSV infections (6% versus 42% of contacts when the goggles were used compared to when they were not). The expense of such goggles will have to be determined and compared with the cost of nosocomial infections. The study has an orgy of confounders, is it difficult to see how such studies can be carried out without disrupting patient care? Why not randomise staff to goggles or standard care?

Gwaltney 1980

Methods	The study assessed the effectiveness of aqueous iodine applied to the fingers in blocking hand transmission of experimental infection with rhinovirus from one volunteer to another. Healthy, young adult volunteers were recruited from the general population at the University of Virginia, Charlottesville. Volunteers were not informed about the contents of the hand preparation until after the study. Two experiments were conducted to evaluate the virucidal activity of aqueous iodine applied to the fingers immediately before viral contamination. Other two experiments were conducted to determine whether there was sufficient residual activity of aqueous iodine after 2 hours to interrupt viral spread by the hand route. Volunteers who were donors of virus for the hand exposures were challenged intranasally on three consecutive days with strain HH rhinovirus. Recipients were randomly assigned to receive iodine or placebo. The donors contaminated their hands with nasal secretions by finger to nose contact before the exposure. Hand contact was made between a donor and a recipient by stroking of the fingers for 10 sec. Donors and recipients wore masks during the exposure period
Participants	15 and 20 volunteers in two experiments
Interventions	Treatment of fingers with iodine versus placebo. The virucidal preparation used was aqueous iodine(2% iodine and 4% potassium iodide). The placebo was an aqueous solution of food colours
Outcomes	Experimental rhinovirus infection reduced (P = 0.06) Laboratory: serological evidence Effectiveness: rhinovirus infection (based on serology, isolation and clinical symptoms) with high score clinical illness. Score was published elsewhere Safety: N/A
Notes	Risk of bias: High (poor description of randomization process, concealment, or allocation) Notes: the study suggests that aqueous iodine applied to the fingers was effective in blocking transmission by hand contact of experimental infection with rhinovirus for up to 2 hours after application (1 out 10 volunteers were infected compared to 6 out of 10 in the placebo preparation arm, P = 0.06 with Fisher's exact test). The effectiveness of iodine treatment of the fingers in interrupting viral transmission in volunteers recommends its use for attempting to block transmission of rhinovirus under natural conditions. Although the cosmetic properties of 2% aqueous iodine make it impractical for routine use, it can be used as an epidemiologic tool to study the importance of the hand transmission route and to develop an effective cosmetically acceptable hand preparation. A summarily reported study

Hall 1981a

Methods	Cohort study to determine the possible modes of spread a RSV to young adult volunteers working on a paediatric ward who were exposed in different manners to infants with RSV. Volunteers were divided into three groups: "cuddlers", exposed to an infected infant over two to four hours by caring the baby in the usual manner, wearing gowns, but no mask or gloves; "touchers", exposed with the infant out of the room by touching surfaces contaminated with the baby's secretions; "sitters", exposed to an infected baby by sitting at a distance of more than 6 feet from an infant's bed, and they wore gowns and gloves, but no masks. In order to control for possible differences in infectivity among infants, a volunteer from each of the three groups was exposed to each infant, or to this environment in the case of touchers. In addition, volunteers from each group were exposed to more than one infant. After exposure volunteers were followed for 12 days
Participants	31 Volunteers: seven in the cuddler group, 10 in toucher group and 14 in the sitter group
Interventions	Exposure to infants admitted with bronchiolitis or pneumonia during a community outbreak of RSV isolation
Outcomes	Laboratory: serological evidence Effectiveness: RSV infection demonstrated by viral isolation and serology. Clinical symptom diary collected with questionnaires. Symptomatic, asymptomatic and febrile symptomatic data reported separately Safety: N/A
Notes	Risk of bias: low Notes: the authors concluded that the spread of RSV may occur by close contact with direct inoculation of large droplets or by self-inoculation after touching contaminated surfaces. Infections does not appear to occur after more distant contact requiring small particle aerosols (0 infected out of 14 "sitters", those that sat away from RSV infected infants, compared with 5 out of 7 who cuddled and 4 out of 10 who touched the infected infants). Ancillary procedures that may be helpful include the care of contaminated surfaces and gowns, cohorting of staff and infants, and limiting the traffic in and out of the infants' room. With limited facilities, isolation rooms might best be reserved for uninfected infants with underlying disease who, should they acquire nosocomial RSV infection, are at risk for severe disease

Hall 1981b

Methods	Controlled before and after study designed to evaluate the efficacy of infection-control procedures with the use of masks and gowns compared with procedures not using mask and gowns on the rate of nosocomial RSV infection in both infants and staff. The study, conducted at Strong Memorial Hospital in Rochester, NY, USA, in 1979, was begun 12 days after the hospital admission of the first infant infected by RSV, and was continued for the next two months. All patients and staff on the ward for children less than three years of age were included. During the first four weeks (period 1) of the study the infection-control procedures for infants with respiratory illness included handwashing and the use of mask and gowns by the staff on entering the room, with a change of gowns between contacts with each infant. After four week the wearing of gowns and masks was discontinued and handwashing alone was used for the final five weeks of the study. Throughout the study handwashing, cohorting and isolation were employed and emphasised. The number of nosocomial infections in patients and staff for period 1 were compared with the period 2 (last four weeks of the study). Infections occurred in the interval week were not counted
Participants	162 patients suspected with RSV infections from infected infants; 78 admitted in the period 1 and 84 in period 2. The age range was 2 weeks to 3 years. 55% were male. Of 78 (period 1), 24 were admitted for RSV infections and the remaining 24 became the contacts. (Due to lack of comparability of children and an unclear text children data were not extracted). 39 ward personnel were included, 30 in the period 1 and 27 of these were also studied during period 2 along with 9 other personnel. Thus a total of 36 staff members were studied during period 2

Interventions	Use of gowns and masks and standard infection-control procedures (handwashing, cohorting, isolation) versus standard infection-control procedures only to prevent transmission of RSV infections from infected infants
Outcomes	Laboratory: serological evidence Effectiveness: RSV infection demonstrated by symptoms, viral isolation and serology Safety: N/A
Notes	Risk of bias: high Notes: The authors concluded that the use of masks and gowns as additional infection-control procedures for RSV infection shows no appreciable benefit in preventing nosocomial spread of RSV to infants or to the ward personnel. The nosocomial infection rate in the two periods was not significantly different in either the infants or staff (32% infection versus 41%). Both of the study periods appeared to be equal in terms of potential for transmission or exposure to RSV. The number of infants admitted during both periods was similar. Furthermore these two groups of contacts were alike in age and types of underlying diseases. The routine use of masks and gowns does not seem warranted in view of the considerable cost. A very poorly reported study with an unclear eligibility procedure and a lack of description of denominators. Why not use randomisation?

Heymann 2004

Methods	Controlled before and after study to evaluate the effect of school closure on the occurrence of respiratory infection among children ages 6-12 years and its impact on health care services. The study was conducted in Maccabi healthcare services, which has a nationwide network of > 3000 independent physicians connected by a unified computer system. The authors assembled a retrospective cohort of all 6 to 12 year old children comprising 186,094 children. The computerised data were examined for three 2-weeks periods: before school closure, during closure, and after closure. The occurrence of respiratory tract infections was determined according to recorded diagnoses, including cough, upper respiratory tract infection, common cold, sore throat and viral infection
Participants	186,094 children aged 6 to 12 years
Interventions	Effect of a school closure on the occurrence of respiratory infection during an "influenza" outbreak
Outcomes	Laboratory: no Effectiveness: respiratory tract infections Safety: N/A
Notes	Risk of bias: high Notes: The authors concluded that school closure was temporally associated with 42% decreased morbidity from respiratory tract infections, a consequent 28% decrease in visits to physicians and to emergency departments and a 35% reduction in purchase of medications. Limits of this study are: the fact that in Israel 33.8% of the population are children, hence these results may not be applicable to Western countries with lower per centage of children. In addition there may be a difference in parental attitudes toward respiratory illness symptoms in other cultures that affect health care utilization. Another reason for such a difference may be the basic structure of the health system in Israel, where comprehensive health insurance is universal and provided by the law. Finally there is limited availability of over-the-counter medications, and to obtain symptomatic therapeutic agents children are generally seen by a physician. The biggest limit to this study is not mentioned by the authors: the assumption that the circulation of respiratory viruses is constant throughout the study period. Although in the Discussion the authors mention some surveillance data on national diffusion of an H3N2 epidemic but this took place in Dec 1999 Observed effect may be due to school closure or they may be due to lower circulation of the viruses

Isaacs 1991

Methods	Retrospective prospective cohort study was conducted to evaluate the effectiveness of cohorting and educational program (handwashing) in reducing the incidence of nosocomial respiratory syncytial virus infections. Data on all children with RSV infection on any of the paediatric wards in winter of 1986-7 were retrospectively collected. In order to define the population at risk of developing RSV infection it was determined the number of children under 2 years of age hospitalised on the two paediatric wards and the paediatric intensive care unit and the number they spent in hospital. For the next two winters (1987 to 1988 and 1988 to 1989) the same data were prospectively collected. In addition some interventions were made to try to reduce the incidence of hospital acquired RSV infection. Children admitted with suspected RSV infection were nursed in a specific area until the result of an indirect immunofluorescent test. It was not possible to cohort babies on the paediatric intensive care unit. Staff were instructed on the importance of handwashing and this was reinforced on ward rounds. An educational leaflet was prepared and given to the parents of every child admitted with the infection
Participants	Children < 2 years of age: 425 in period 1; 840 in period 2; 552 in period 3
Interventions	Isolation and handwashing versus normal care
Outcomes	Laboratory: indirect immunofluorescence on nasopharyngeal secretions or by culture of secretions Effectiveness: RSV infection Safety: N/A
Notes	Risk of bias: high (poor descriptions) Notes: the authors concluded that hand washing and cohorting reduced at least 66% in the number of hospital acquired infections due to RSV in the two intervention winters. One minor problem with cohorting was that babies could not remain in the accident and emergency department until a diagnosis of RSV was virologically confirmed. Hence they were cohorted on the basis of a clinical diagnosis of bronchiolitis. The authors also underline the importance of a more rapid antigen test for RSV. It is doubtful whether the non-exposed cohort is similar to its hospital peers, especially because there are several cardiac children in the exposed cohort. The biggest limit to this study is mentioned by the authors in the Discussion: the assumption that the circulation of RSV is constant throughout the study period. Exposure however is not the same in the 3 seasons and observed effect may be due to cohorting or to the different viral circulation

Kimel 1996

Methods	Prospective cohort study conducted in a school of Chicago, USA, to evaluate the effectiveness of a handwashing program in reducing the absenteeism caused by flu-like illness. The school was located in a predominantly white, middle to upper middle class suburb. All four kindergarten and five first-grade classes were included in the study. No significant differences were found between participating classes for size, male-female ratio, percentage of low-income students, or students with chronic health problems. Teachers were surveyed to determine classroom handwashing activities. The influenza season usually occurs during December and January. The handwashing program was planned for presentation just prior to this time. The effectiveness of the program was determined by comparing absentee rates among participants and non participating classes (the control group). Absentee rates were determined by reviewing the computerized daily school absence logs. Entries that listed flu-like symptoms were counted. A take-home handwashing chart was also given to each student to encourage follow-through with handwashing at home
Participants	199 children of kindergarten and first grade schools
Interventions	Handwashing and educational program versus no intervention
Outcomes	Laboratory: no

Kimel 1996 (*Continued*)

	Effectiveness: flu-like illness Safety: N/A Absenteeism from influenza-like illness was approximately double in the control arm (P = 0.01)
Notes	Risk of bias: medium Notes: The authors concluded that hand washing education can decrease absenteeism even among kindergarten and first grade students. This study did not control for health and hygiene practices at home or exposure to flu-like illness outside of school. Furthermore the student population at the school was generally healthy, probably because families were able to provide adequate health and hygiene resources. Another problem of the study is that flu season was later than usual (February), and this represented a confounding variable. The teacher surveys indicated problems with handwashing facilities

Kotch 1994

Methods	Pair-matched cluster randomised controlled trial conducted in the period 19 October 1988 to 23 May 1989 in 24 child care centres in North Carolina, USA. The trial tested the effects of a handwashing and environment sterilising programme on diarrhoea (data not extracted) and ARIs. Child day care centres had to care for 30 children or less, at least 5 of whom had to be in nappies and intending to stay open for at least another 2 years. Randomisation is not described, nor are cluster coefficient reported. Centre were matched in pairs and then randomly allocated to either intervention of control programmes
Participants	389 children aged 3 years or less in day care for at least 20 hours a week. There were some withdrawals but the attrition on participants is not stated, only that in the end data for 31 intervention classrooms and 36 control classrooms were available. There were 291 children aged up to 24 months and 80 over 24 months that took part. The text is very confusing as 371 seem to be the total of the number of families that took part. No denominator breakdown by arm is reported and numerators are only reported as new episodes per child-year
Interventions	Structured handwashing and environment (including surfaces, sinks, toilets and toys) disinfecting programme with waterless disinfectant scrub
Outcomes	Laboratory: N/A Effectiveness: ARI (coughing, runny nose, wheezing, sore throat or earache) Safety: N/A
Notes	Risk of bias: high (poor reporting of randomization; outcomes; numerators; and denominators) Notes: the authors conclude that the fully adjusted RR for prevention of ARIs was 0.94 (-2.43 to 0.66). A poorly reported study

Krasinski 1990

Methods	Controlled before and after study conducted in Bellevue Hospital Center, New York, USA, to determine the effectiveness of screening for RSV and assignment to a cohort at admission to reduce nosocomial transmission of RSV infections. Children who were 3 years of age and older were admitted to a paediatric ward that is equipped with private rooms for the control of communicable diseases. Children younger than 3 years of age were admitted to a separate ward without private rooms, where as many as four children shared a room. All paediatric patients hospitalised on or before Dec 31 1986 were regarded as potentially infected with RSV and were constituted as an RSV-infected cohort. A second cohort, free of infection with RSV, was established on the toddlers' ward to segregate high risk patients from

Krasinski 1990   (*Continued*)

RSV-infected patients. Patients requiring hospital admission and assignment to the high risk cohort were screened for evidence of RSV infection by means of a rapid ELISA method. No gloves or masks were used in the RSV cohort

Participants	All hospitalised paediatric patients regarded as potentially infected with RSV
Interventions	RSV screening cohorting and service education programme versus do nothing
Outcomes	The authors concluded that screening and subsequent cohorting reduced RSV infections (from 5.33 infections per 1000/patient days of care to 1.23 infections per 1000/patient days after introduction of screening). There was an attempt at correlation between RSV admissions and RSV community circulation
Notes	Risk of bias: medium Notes: the authors concluded that screening and subsequent cohorting reduced RSV infections (from 5.33 infections per 1000/patient days of care to 1.23 infections per 1000/patient days after introduction of screening). There was an attempt at correlation between RSV admissions and RSV community circulation

Krilov 1996

Methods	Controlled before and after study carried out in a 16 classrooms of special needs school for Down syndrome children in New York State. The study took place between November 1991 to November 1993. The before between Nov 1991 and Oct 1992, followed by a one month washout period during which the intervention was introduced, followed by 12 months of after period (Dec 1992 to Nov 1993)
Participants	Thirty three children aged 6 weeks to 5 years took part in the before and 38 in year 2 (after period). During the study period there were about 110 children in the school but the parents of the majority did not agree to replying to 2 weekly questionnaires, so their children were not entered in the study. In addition 5 sets of questionnaires in the before and 2 in the after periods did not contain sufficient data (6 months' worth) and were excluded. Despite this there were no significant differences between before and after children. The authors also describe viral circulation during the study periods from isolates in the local hospital. All community isolates were constant with the exception of adenovirus which doubled in the after period of the study
Interventions	Training and sanitary programme with handwashing, disinfection of school buses, appliances and toys. In addition a person designated a study monitor carried out intensive monitoring of classroom behaviour and reinforced messages. Disinfection took place with Reckitt & Colman products (sponsors of the study)
Outcomes	Laboratory: viral isolates from surrounding community (non random samples) Effectiveness: ARI (cough, runny nose, sore throat, wheezing or rattling in the chest, ear ache). Vomiting and diarrhoea (data not extracted). Follow up was carried out on the basis of parents' questionnaire Safety: N/A
Notes	Risk of bias: high (disinfectants provided and study sponsored by manufacturer) Notes: The authors concluded that respiratory illnesses decreased from a median of 0.67 to 0.42 per child per month (P < 0.07), physician visits, 0.50 versus 0.33 (P < 0.05), mean course of antibiotics prescribed 0.33 versus 0.28 (P < 0.05) and days of school missed because of respiratory infections 0.75 versus 0.40 (P < 0.05). Respiratory illnesses decreased from a median of 0.67 to 0.42 per child per month. Small study with a serious selection bias and generalisability problems

Ladegaard 1999

Methods	RCT with cluster randomisation (they called it "lottery", the same as "clip the coin") to intervention or control. Out of 10 institutions they excluded two because they want institutions comparable in uptake area (that means housing and income). Interventions were given to children, parents and teachers at the institutions
Participants	Children 0 to 6 years old
Interventions	Multifaceted: information, t-shirts to the children with: "Clean hands - yes, thank you", performance of a fairytale "The princess who did not want to wash her hands", exercise in hand washing, importance of clean and fresh air. The aims of the intervention were: - to increase the hygiene education of the day care teachers - to motivate the children by practical learning to have a better hand hygiene - to inform the parents about better hand hygiene
Outcomes	34% decrease in 'sickness', (probably mostly gastroenteritis)
Notes	Risk of bias: limited data only available Notes: the authors conclude that there was a 34% decrease in sickness in the intervention arm, this is probably overall sickness as gastroenteritis is part of the outcomes (data no extracted). Limited data only available from translation by Jørgen Lous

Lau 2004a

Methods	Case-control study carried out in Hong Kong, SAR of China during 4 April to 10 June 2003, at the height of the SARS outbreak. The aim was to describe the defined and undefined sources of SARS cases groups and assess the protective effects of various public health measures. Defined sources were classified as being a healthcare worker in a hospital, living in Amoy Gardens (a known focus of infection) having had a contact with a member of the household with SARS of earlier onset, hospital in patients infected with SARS by other hospital inpatients and contacts of SARS cases before the onset of their own symptoms. The undefined sources group of cases were all the other categories. Cases in general were identified and interviewed on the phone. Households with more than one index case were considered as having two index cases. Of the 1690 identified cases, 1214 from 996 households were enrolled in the study. One hundred and forty cases could not be contacted as they had a wrong phone number, 163 were uncontactable after at least five attempts, 163 refused to take part and 10 did not speak either Chinese or English. Seventeen were further excluded because they were aged less than 16. Twenty two questionnaires were unusable. (This makes 1175, obviously the 17 minors are included in the case-control study, as adding them makes a total of 1192)
Participants	Description of cases: 330 probable cases of SARS selected as follows. From 1192 people with probable SARS reported to the Department of Health in the territory of HK up to 16 May 2003, 1175 were entered in the case-control analysis. SARS cases were defined as RX evidence of pulmonary infiltration consistent with pneumonia with a temperature of > 38 C or a history of such in the previous 2 days and at least 2 of the following: history of chills in the previous 2 days new or increased cough, breathing difficulty, general malaise of myalgia, typical signs of consolidation and known exposure to SARS. The authors say that this definition is the same the WHO's case definition of probable SARS. At interview, risk factors were elicited and identified. There were 727 cases in the defined source category and 347 in the undefined sources category (330 after exclusion of 17 minors) Description of controls: 660 controls of undefined origin and with no description of selection
Interventions	Natural exposure to SARS during a serious epidemic
Outcomes	Community transmission of SARS reduced OR 0.30 (95% CI 0.23 to 0.39)

Lau 2004a   (*Continued*)

Notes	Risk of bias: medium (inconsistencies in the text: lack of description of controls)
	Notes: the authors conclude that community transmission was of less importance than previously thought and public health measures worked. The following risk factors were significantly associated with SARS (matched multivariate analysis OR with 95% CIs):
	- Visit to mainland China 1.95 (1.11 to 3.42)
	- Visited Price of Wales Hospital 7.07 (1.62 to 30.75)
	- Visited other hospitals 3.70 (2.54 to 5.39)
	- Visited Amoy Gardens 7.63 (3.77 to 15.43)
	The following activities/interventions had a significant protective function:
	- Thorough disinfection of living quarters 0.41 (0.29 to 0.58)
	- Wore a mask in public places frequently 0.36 (0.25 to 0.52)
	- Washed hands 11 or more times a day 0.58 (0.38 to 0.87)
	Potentially a very interesting study possibly rigorously conducted let down by a very confusingly written text. The biggest problem is lack of clarity as to who the controls were. This may be a reflection of the pressure of carrying out a study in the midst of a serious epidemic

Leclair 1987

Methods	Controlled before and after study conducted in Children's hospital of Boston, USA, to determine whether increased compliance with a policy of glove and gown isolation precautions could reduce the high rate of nosocomial RSV infection on an infant and toddler ward. All patients admitted to the 28-bed infant and toddler medical ward during three consecutive RSV seasons (1982 to 1985) were included in the study. When patients with known or suspected RSV infection were admitted, an attempt was made to place them in single rooms or to group them together, but infected patients were frequently required to share rooms with susceptible patients during the winter months, when the prevalence of RSV on the wards is highest. The RSV season was defined as the 24 weeks each year starting at the beginning of November and continuing through the end of April. All the documented cases of RSV infection occurred during that period, and all the patients and patient-days during that interval on the study ward were recorded. RSV infections were classified as nosocomial if symptoms developed five or more days after the patient's admission to the hospital. All cases of RSV infection were confirmed virologically. During the first half of the study nursing staff wore both gloves and gowns for only 20 of 52 observed contacts. During and after the second compliance survey, compliance rapidly increased: nursing staff wore both gloves and gowns for 73 of 90 of their contacts
Participants	695 patients aged from 5 days to 4 years and 11 months. The distribution of ages was similar in the two periods. Thirty-seven acquired nosocomial RSV infections
Interventions	Infection-control intervention to increase use of gloves and gowns versus no intervention
Outcomes	Laboratory: yes
	Effectiveness: RSV infection
	Safety: N/A
Notes	Risk of bias: low
	Notes: The authors concluded that the incidence of nosocomial RSV infection rose with the intensity of hospital exposure and that this rise was markedly different in the periods before and after intervention. The use of gloves and gowns can reduce the nosocomial transmission of RSV, particularly with increasing exposure to patients shedding the virus (RR for pre and post intervention periods infection rates 2.9, 1.5 to 5.7). Compliance by the staff improved dramatically after the intervention and it continued even after the end of the study, probably because the favourable results of the intervention were well publicized, the head nurse introduced an educational program emphasising the appropriate application of isolation precautions, and gowns and gloves became more accessible to care givers. The

Leclair 1987 (*Continued*)

study, although prone to selection bias, is better designed than some of it peers as there is an attempt at adjusting for different levels of RSV circulation by sub-analysis by virus shedding days by the infected participants

Leung 2004

Methods	Prospective cohort study conducted during 13 March to 29 June 2003 in the paediatric department of the Price of Wales Hospital at the height of the SARS epidemic in Hong Kong, China. The aim of the study was to test the effectiveness of procedures to stop transmission of SARS from infected children to carers and visitors
Participants	26 HCWs in close contact with probable or suspected SARS and 88 HCWs in contact with patients in other study areas during the study period
Interventions	Triage and UHR-S isolation & strict infection control procedures versus triage and UHR-S isolation and less strict infection control procedures. Healthcare workers were exposed to nine children with probable SARS and 29 with suspected SARS admitted into the Ultra High Risk SARS (UHR-S) areas with a mean age of 8.9 years, 88 children with pneumonia but no SARS contact with a mean age of 8.2 admitted to the isolation cubicle of the Ultra High Risk Infection (UHR-I) area, 227 with febrile illness and normal chest radiograph aged 4.9 years treated in an open cubicle in the UHR-I area and 274 non febrile children with a mean age of 7.5 years admitted into the High Risk (HR) area. The study tested the effectiveness of triage and UHR-S isolation + strict infection control procedures vs triage and UHR-S isolation + less strict infection control procedures. Triage at admission aimed at identifying children aged less than 18 who: were febrile or afebrile with a known SARS contact who were admitted to the UHR-S area with a positive CXR and a SARS contact who were admitted to the UHR-S area with CXR changes but no SARS contact who were admitted to the UHR-I area were febrile or afebrile but no SARS contact who were admitted to the HR area Very strict infection control measures were implemented on entry and exit from the UHR-S area (handwashing, gown, caps, goggles, mask , upper and trousers of cloth operating theatre garments and N95 face respirator for HCWs, all measures but no goggles or undergarments for visitors and handwashing and mask for patients). Less strict infection control measures were implemented on entry and exit from the UHR-I area (handwashing, gown, goggles, mask , upper and trousers of cloth operating theatre garments and N95 face respirator for HCWs, and handwashing and mask for visitors and patients), Even less strict infection control measures were implemented on entry and exit from the HR area (handwashing, gown, caps, goggles, mask , upper and trousers of cloth operating theatre garments and mask of N95 face respirator for HCWs and handwashing and paper mask for visitors and patients). Enforcement was directed by a police nurse in the UHR areas
Outcomes	Laboratory: laboratory confirmation of SARS Effectiveness: probable or suspected SARS according to WHO definitions Safety: N/A
Notes	Risk of bias: low Note: rhe authors conclude that the measures worked well as no HCW or visitor became ill. This is a remarkably well-conducted and clearly reported study in the midst of a major infectious disease outbreak with a previously unknown agent. The Prince of Wales Hospital had previously witnessed an outbreak in which an index patient had infected 138 health care workers. All the more remarkable as the paediatric department had not been built as isolation facility and had to be rapidly reorganised.

Longini 1988

Methods	Cluster-controlled double blind randomised trial to assess the efficacy of virucidal tissues in interrupting family transmission of rhinovirus and influenza virus. The study was carried out in the community of Tecumseh, Michigan, USA during the period 25 November 1984 to 28 April 1985. However, the authors only report results for the period 13 January to 23 March 1985, when a high circulation of influenza A H3N2 and rhinovirus was detected
Participants	296 households were enrolled but for "technical reasons" five household were eliminated from the analysis. The analysis was carried out in households with 3 to 5 members. The authors report data on 143 households randomised to virucidal tissues and 148 to placebo tissue. Average age in households was around 22 and the difference between arms was not significant. Randomisation was carried out by the sponsor and tissues were pre-packed in coded boxes with no other identifying features and delivered to households at the beginning of the study period
Interventions	Disposable three-layered virucidal tissues (citric and malic acids with sodium lauryl sulphate in the middle layer) or placebo (succinic acid in the middle layer) tissues. They were used to blow the nose, coughing or sneezing into. Households were also stratified by level of tissue use. Tissue use was significantly higher in the intervention arm (82% versus 71%)
Outcomes	Laboratory: yes - viral culture from nasal and throat swabs from symptomatic participants Effectiveness: ARI (with a proportion of laboratory confirmed diagnosis in non randomly chosen participants with symptoms lasting 2 days or more) Follow up and surveillance was carried out using a telephone questionnaire Safety: N/A
Notes	Risk of bias: high (inappropriate choice of placebo) Notes: the authors conclude that virucidal tissues were up to 36.9% effective in preventing transmission of ARIs as measured by secondary attack rates (18.7% versus 11.8%). This was not significant but may well have been affected by the lack of do-nothing community controls. This a well-designed, well written study despite the unexplained attrition of 5 families, the lack of reporting of cluster coefficients and the differential in tissue use between the two arms which raises questions about the robustness of double blinding. Particularly notable is the discussion on the low generalisability of results from the study from the placebo arm given that even the inert barrier of the tissues is a likely to have limited spread. Also the lengths to which the authors went to obtain allocation concealment and maintenance of double-blind conditions

Luby 2005

Methods	Partly double blind cluster randomised controlled trial carried out during 15 April 2002 to 5 April 2003 in Karachi, Pakistan. The trial assessed the effects of mother and child handwashing on the incidence of respiratory infections, impetigo (data not extracted) and diarrhoea (data not extracted). Randomisation took place by computer generated random numbers in three phases: - 25 neighbourhoods were assigned to handwashing and 11 to standard practice - 300 households assigned to using antiseptic soap - 300 households assigned to using plain soap - 306 households assigned to standard practice - 1523 children younger then 15 years assigned to using antiseptic soap - 1640 children younger then 15 years assigned to using plain soap - 1528 children younger then 15 years assigned to standard practice Soaps were identical weight, colour, and smell and were packed centrally with a coded packing case matched to households containing 96 bars. Neither field workers not participants were aware of the content. Control arm households were visited with the same frequency as intervention household but were given books and pens. Codes

Luby 2005 (*Continued*)

	were held centrally by the manufacturer and broken after the end of the trial to allow analysis
Participants	Householders of slums in Karachi. Of the 1523 children younger then 15 years assigned to using antiseptic soap 117 dropped out (1 died, 51 were born in and 65 aged out) = 1406; 504 were aged less than 5 Of 1640 children younger then 15 years assigned to using plain soap 117 dropped out (3 died, 44 were born in and 70 aged out) = 1523; 517 were aged less than 5 1528 children younger then 15 years assigned to standard practice 125 dropped out (3 died, 40 were born in and 82 aged out) = 1403; 489 were aged less than 5
Interventions	Instruction programme and antibacterial soap containing 1.2% triclocarban, or ordinary soap to be used throughout the day by householders or standard procedure
Outcomes	Laboratory: N/A Effectiveness: - Number of new respiratory illness per person per week - Pneumonia (cough or difficulty in breathing with a respiratory rate of > 60 min in children less than 60 days old, > 50 min in those less than 1 year old and > 40 min for those aged 1 to 5 years) Follow up was weekly with household interview and direct observation. Children aged less than 5 were weighed and the report presents stratification of results by child weight Safety: N/A
Notes	Risk of bias: low (cluster coefficients and analysis by unit of randomization provided) Notes: The authors conclude that "handwashing" neighbourhoods has significantly less episodes of respiratory disease than controls (e.g. 50% less cough). "Handwashing" children aged less than 5 had 50% less episodes of pneumonia than controls (-65% to -35%). However there was no difference in respiratory illness between types of soap. The report is confusing, with a shifting focus between children age groups. The impression reading is of an often re-written manuscript. There is some loss of data (for example in the results by weight, i.e. risk group) because of lack of clarity on denominators. Despite this, the trial is a landmark

Macartney 2000

Methods	Controlled before and after study with economic evaluation (data not extracted) carried out over 8 RSV seasons in 1988 to 1996. The study assessed the impact of a programme for the interruption of transmission of RSV in a children hospital in Philadelphia, USA. Analyses are presented both by risk group (exposure to patients by days of viral shedding) and as aggregate. Only for the latter numerators and denominators are provided, whereas for the former figures are presented in bar chart format
Participants	Children with community-acquired RSV infection and the inpatient children exposed to them (1604 in 4 seasons before and 2065 in the "after the intervention" seasons. Children were aged around 1 year and those with risk factors were equally spread (51% versus 54%) in the two periods
Interventions	Education with high index of suspicion for case-finding with barriers (but no goggles or masks) and handwashing for patients and staff with contact precautions for RSV + patients for 2 weeks with isolation (when possible) with cohorting of patients and staff with enhanced surveillance with restriction of visits with discouragement of staff with ARIs from working unprotected in SCBU
Outcomes	Laboratory: ELISA confirmation of RSV infection on all children admitted with respiratory symptoms. In a proportion of cases RSV culture was undertaken, although this had a minimal practical impact as any child with respiratory symptoms was considered as a RSV case Effectiveness: clinically defined RSV cases contracted nosocomially (with symptoms appearing after at least 6 from

Macartney 2000 (*Continued*)

	admission Safety: N/A
Notes	Risk of bias: low Notes: the authors conclude that 10 RSV infections were prevented per season (RR for post-intervention compared to pre-intervention periods 0.61, 95% CI 0.53 to 0.69). The study is well reported and the conclusions appear reasonable, but no information is given on the background rate of infection and the impact of the intervention on HCW morbidity is not analysed

Madge 1992

Methods	Prospective cohort study conducted in 4 medical wards of the Royal Hospital for Sick Children in Glasgow, UK, to evaluate the effectiveness of 4 infection control procedures in preventing nosocomial infection with RSV. This is an interruption of transmission study. Every child up to 2, irrespective of clinical presentation, had respiratory secretions tested for RSV antigen within 18 hours of admission. Nosocomial infection was assumed if a child become RSV positive 7 days or more after admission. Children after discharge from hospital were not studied
Participants	No special precaution group 152 (winter 1); gowns/gloves 337 (winter 1 and 2); cohort nursing 265 (winter 1 and 2); cohort nursing and gowns/gloves 310 (winter 1 and 2); 1001 (winter 3)
Interventions	Stepwise intervention programmes: gowns/gloves; cohort nursing+gowns/gloves; cohort nursing, versus no special precautions. The procedures evaluated in the two winter periods were gowns/gloves; cohort nursing+gowns/gloves; cohort nursing, versus no special precautions. In the third year the most effective strategy was introduced into all ward areas and its efficacy in clinical practice was assessed. There was not separate area for managing children with infections
Outcomes	Laboratory: yes - culture, antibodies titres, serological studies Effectiveness: RSV infections (seroconversion within 7 days of admission) Safety: N/A
Notes	Risk of bias: low Notes: the authors conclude that combined with rapid laboratory diagnosis, cohort nursing and the wearing of gowns and gloves for all contacts with RSV-infected children can significantly reduce the risk of nosocomial RSV infection (odds reduced to between 1.27% to 75.6%). One confounding effect that was not accounted for in the study design was a possible "ward effect". For practical reasons, two wards (3 and 4) continued with the same policy over the first 2 years of the study. Since it was also necessary apply policies to whole wards there is a possibility that ward 4 might have been especially effective at implementing their assigned policy

Makris 2000

Methods	Prospective cohort study carried out in 8 private, freestanding long-term care facilities located in New Jersey and Delaware, to determine the impact of an ongoing infection control intervention program in reducing the incidence of nosocomial infections. The 8 facilities were selected on the basis of similarity with respect to admission rate, size, acuity levels, availability of services, overall infection rates, in-house environmental service departments. Resident populations were comparable in terms of age, sex and underlying disease. The 8 facilities were grouped into 4 sets of matched pairs. Within each pair, each home was designated at random as either a test site or a control site. The results was that 4 facilities (2 urban and 2 suburban, with a total of 443 beds), were selected as test sites and another 4 facilities, 2 urban and 2 suburban, with a total of 447 beds, were selected as control sites

Participants	443 beds (patients) in the test group, 447 beds (patients) in the control group. We assumed number of beds as number of participants.
Interventions	Infection-control education programme reinforcing handwashing and other hygienic measures versus normal care
Outcomes	Laboratory: no Effectiveness: upper respiratory infections Safety: N/A
Notes	Risk of bias: high (internal inconsistencies) Notes: the authors conclude that infection control education measures that reinforce handwashing and other hygienic measures helps reduce the number of organisms present on hands and surfaces and may have contributed to the non significant reduction of URTIs (the opposite is reported in the paper: incidence density rate of 4.15/1000 patient days in the test homes versus 3.15/1000 patient days in the control homes) showed in this study. We assumed number of beds as number of participants to the study, but we don't know the characteristics of the patients (age, sex, underlying conditions, etc.). The authors confuse a cohort design with a before and after design and in the report they confusingly use both terms and reach conclusions not supported by the evidence presented

Master 1997

Methods	Prospective cohort study conducted in an elementary school, Detroit, to evaluate the effect of a mandatory scheduled handwashing program on absenteeism due to acute communicable illness (including upper respiratory disease). Classrooms were divided into either control or experimental groups without formal randomisation. Six classrooms were assigned to the handwashing group and eight classrooms were assigned to the control group. Data were collected for 37 school days. Information about absent children was recorded daily by the school secretary. Symptoms were used to classify students as having respiratory or gastrointestinal illness. upper respiratory infections and gastrointestinal symptoms (data not extracted) were not considered mutually exclusive
Participants	14 classrooms including 305 healthy, predominantly upper middle-class children ranging from ages 5 to 12. All grade levels from kindergarten through fifth grade were included. Six classrooms (143 students) were the handwashing group and eight classrooms (162 students) were the control group
Interventions	Handwashing program versus usual practice. Children in the handwashing group were asked to wash their hands after arrival at school, before eating lunch, after lunch recess, and before going home. Children in the control group washed at their normal frequency. All children in both groups washed with the school soap, which was not antibacterial.
Outcomes	Laboratory: no Effectiveness: upper respiratory infections (URI) - cough sneeze, pink eye, headache, mononucleosis, acute exacerbation of asthma, sinus trouble, fever alone, bronchitis Safety: N/A
Notes	Risk of bias: high Notes: the authors conclude that handwashing among children can be effective in preventing transmission of disease, but the difference in days of absence is statistically significant only for gastrointestinal symptoms (RR for ARIs 0.79, P = 0.756). Limitations in the study design are: use of a discrete population without socio-economically diverse backgrounds, use of a single institution, lack of blind assessment, low specificity of symptoms, and lack of accurate symptom definition

Morton 2004

Methods	Cross-over study to evaluate the effectiveness of an alcohol gel as an adjunct to regular handwashing for decreasing absenteeism among elementary children by reducing specific communicable diseases such cold, flu and conjunctivitis. The study was conducted in an elementary school in New England, US. In the crossover design classrooms in each grade level were randomised to begin as the experimental group (alcohol gel) or the control group (regular handwashing). A study protocol for hand hygiene was introduced following the germ unit education. The hand washing product was a soap and water alternative that is approximately 60% ethyl alcohol. In phase 1 (46 days) children in 9 classrooms were in the experimental group, and children in 8 classrooms were in the control group. After a 1 week washout period when no children had access to the alcohol gel, Phase 2 (47 days) started, and the classroom that had participated before as an experimental group passed in the control group and vice versa. Data were collected by the parents that informed the secretary or the school nurse of the reasons for a child's absence, including symptoms of any illness. Respiratory illnesses were defined by symptoms of URTI
Participants	253 children, 120 girls and 133 boys, from kindergarten to 3rd grade. 32 children dropped out (10 due to skin irritation and 22 because of lack of parental consent)
Interventions	Use of an alcohol gel as an adjunct to regular handwashing and educational program versus regular handwashing and educational program
Outcomes	Laboratory: no Effectiveness: days of absences from school for respiratory illness Safety: N/A
Notes	Risk of bias: high (no description of randomisation; partial reporting of outcomes, numerators and denominators) Notes: the authors conclude that significantly fewer children became ill while using the alcohol gel as an adjunct to regular handwashing than when using regular handwashing only (decreased school absenteeism of 43% with the use of alcohol gel on top of handwashing). The authors also described, as a limitation of the study, the fact that the school nurse served ad the data collector, and this could be perceived as bias in measurement of the outcome variable. Randomisation and allocation are not described, there are no cluster coefficients reported and attrition is not taken into consideration during the analysis. Unit of randomisation and analysis are different. No reporting by arm. No ORs, no CIs reported

Murphy 1981

Methods	Prospective cohort study carried out in the Children's Hospital, Denver, to examine the effect of using gowns, masks and handwashing on the acquisition of symptomatic respiratory infections by medical personnel caring for infants with respiratory disease
Participants	58 people of nursing, medical, respiratory therapy personnel; 30 in the handwashing group, 28 in the handwashing, masks and gowns. Seventy HCWs initially were available for enrolment, 9 refused to take part and 3 withdrew
Interventions	Handwashing versus handwashing, masks and gowns
Outcomes	Laboratory: yes Effectiveness: viral infections (including RSV) Safety: N/A
Notes	Risk of bias: medium Notes: the authors conclude that there was no difference between the two groups with respect to number of viral infections (i.e. 4/30 in the handwashing group versus 5/28 in the handwashing gown and masking group (P >0.20).

Murphy 1981   (*Continued*)

The findings cannot demonstrate any effect of adding the use of both gown and mask to the usual handwashing routine on the development of illness in personnel caring for infants with respiratory disease. Possible reasons for lack of effect are: the heavy exposure all adults have to respiratory viral illness in the community at large; poor compliance to the study protocol, modes of virus spread which would not be blocked by the use of mask and gown

Niffenegger 1997

Methods	Prospective two-centre cohort study assessing the effects of a handwashing programme in Indiana, USA. Two centres were enrolled for the August to December 1994 (21 weeks) study: a test and a control centre
Participants	Eight teachers and 26 children (aged 3 to 5) in the test group and 12 children and 8 teachers in the control group. According to the authors, age, experience gender and socioeconomic variables were equally distributed between the two groups, but data are not shown. No attrition is mentioned
Interventions	Three weekly cycles of teachings, handwashing routine encouragement for children, parents and staff and correct sneezing and coughing procedure. Follow up was weekly filling in of a teacher report. It is unclear from the text what happened in the control site, or indeed if they were fully aware of the project
Outcomes	Laboratory: N/A Effectiveness: colds and ARIs no better defined Safety: N/A
Notes	Risk of bias: high (wide range of incidence of infections) Notes: the authors conclude that during the first 11 weeks of the study the test centre had double the incidence of colds compared to the control centre this is explained by the author as caused by the influx of new children bringing in new viruses in the test centre. In the second period the reverse was true, explained as the stabilising of the population and the taking effect of the programme. The list of potential confounders and biases is countless. For example there is only a very cursory description of participants in both arms and the role of teachers especially in the control centre is not explained.

Nishiura 2005

Methods	Case-control study carried out during the SARS outbreak (26 Feb 03 to 28 Apr 03) in Hanoi, Vietnam. The study aimed at assessing the relationship between SARS infection and behaviour. The study population was based at the Hanoi French Hospital (HFH) and followed the outbreak during three phases. The first phase (26 Feb to 4 Mar 06) in which an index case and 9 suspected secondary cases were admitted/cared for. The second phase (8 Mar to 11 Mar 03) in which outpatients were closed and staff no longer returned home as the outbreak spread and the third phase (11 Mar 03 to 28 April 03) in which the HFH was closed to all other then SARS cases who were isolated
Participants	Description of cases: 29 surviving people with laboratory confirmed SARS cases either admitted and retained or transferred to other hospitals. Nine cases did not take part (5 died, 1 refused and 3 had relocated). Twenty eight were HCWs employees of the HFH and 1 a relative of a patient. Substantial exposure and behaviour were documented through observation and questionnaires Description of controls: 90 people aged > 20 who provided written consent with substantial SARS exposure, 57 of whom were HFH employees

Nishiura 2005   (*Continued*)

Interventions	Handwashing before contact with SARS patient Handwashing after contact with SARS patient Masks Gloves Gowns All measures combined Analysis by epidemic stage is reported
Outcomes	SARS infection
Notes	Risk of bias: low Notes: the authors conclude that masks (OR 0.3, 95% 0.1 to 0.7) and gowns (OR 0.2, 95% 0.0 to 0.8) were significantly associated with protection (OR, 95% to) during phase 1 but in Phase 2 masks (OR 0.1, 95% 0.0 to 0.3) and all measures (OR 0.1, 95% 0.0 to 0.3) were associated with protection probably because of the increased awareness of the danger of the outbreak and increase us of measures - this is confirmed by the results of the mathematical model in the second part of the study. A well written and reported study

Ou 2003

Methods	Retrospective cohort study carried out in selected precincts of Haidian district of Beijing, People's Republic of China between March and May 2003 during the epidemic of Severe Acute Respiratory Syndrome (attack rate 19/100,000 population in the period March to July). Precincts were chosen on the basis of the highest number of quarantinees. The study aimed at assessing the risk of acquiring SARS among quarantinees. A better definition of the risk would help in future to identify better candidates for quarantine and target resources accordingly. The study was based on a questionnaire-based survey on the reasons for quarantine. SARS diagnosis for contacts was independently carried out from lists
Participants	171 SARS cases (29% of total) were identified in the precincts and 1210 persons (23%) quarantined from the selected districts (contacts). These were sampled from a total population of 2.24 million, with 5.186 quarantinees. Response rate was 85% (1.028 quarantinees who completed the questionnaire, of which 232 developed probable SARS while in quarantine)
Interventions	Quarantine at home or hospital for 14 days post-exposure (reduced to 10 and then to 3). Quarantine is defined as the separation and or restriction of movement of persons who due to recent exposure to a communicable disease risk acquiring the disease and transmitting to third parties. A contact was defined as: - Health care worker not using personal protective equipment (PPE) when caring for/assessing a SARS case; - other persons caring for a SARS case - persons sharing accommodation with a SARS case - persons visiting a SARS case - persons working with a SARS case - classmates or teachers of a SARS case - persons sharing the same means of public transport with a SARS case All quarantinees were followed-up daily and were admitted to hospital if they developed fever (38 C or more)
Outcomes	Laboratory: no Effectiveness: definition of SARS was based on criteria of Chinese Ministry of Health. Definition was clinical and not based on laboratory isolation of the SARS-CoV Safety: N/A

Ou 2003   (*Continued*)

Notes	Risk of bias: high
	Notes : the authors conclude that only those quarantinees who actually had home or hospital contact with a symptomatic SARS patient developed the illness (attack rate 31.1, 95% CI 20.2 to 44.4 for carers, 8.9%, 95% CI 2.9 to 22.1 for visitors, 4.6%, 95% CI 2.3 to 8.9 for those who lived with a SARS case) but not those living in the same building or working with them and not contacts of any SARS case during the incubation period. Fever was also not a good reason to quarantine people (attack rate nil). Quarantine also appeared to prevent transmission, although there were numerous cases in which quarantine was not required. There several limits to the conclusion of the study. Non random basis for the sample, selection bias of the sample and responders, recall bias of responders and the absence of a laboratory confirmed diagnosis ma have affected the conclusion one way or another.
	Overall, not enough denominator data, non exposed data are given to allow data extraction or calculate OR

Pang 2003

Methods	Ecological study describing and analysing the effects of public health measures on the SARS epidemic between 5 March and 29 May 2003 in Beijing, China. Data were collected from centralised notification and close contact databases
Participants	2521 probable SARS cases mostly hospitalised aged around 33 (407 or 16% were HCWs) and 192 of these who died out of a total population of 13.6 million people. The peak took place on 25 April with 173 hospitalised cases
Interventions	SARS was made notifiable on 9th of April and contact tracing commenced a day later. On 18 April 62,363 of the estimated 85,000 Beijing HCWs received training in the management of SARS cases and were issued gowns, gloves, masks. By 17 April, 123 fever clinics were opened, however these were contiguous to hospitals and it is thought that some transmission occurred.
	By 21 April quarantine of close contacts was underway (these were only allowed to leave quarantine in exceptional circumstances and only wearing a mask) and fever check at airports were begun the day after. By 24 April all schools and universities closed. Two days later public meeting places (bars, libraries etc) were closed. From 27 April all SARS cases were placed in designated hospital wards and by 8 May SARS cases were only sent to designated hospitals. By 1 May a SARS hospital of 1000 beds built in 1 week was opened and received only SARS cases (40% of total cases). The last cases were registered on 26 May. The highest attack rate (14.5%) of quarantined people was those of spouses of SARS cases
Outcomes	Laboratory: laboratory testing for the presence of SARS-CoV was not part of the case definition
	Effectiveness: Probable SARS cases (close contact of a SARS sufferer with signs and symptoms of febrile respiratory disease and chest X-ray changes, or person visiting of residing in an area with recent SARS activity and with signs and symptoms of febrile respiratory disease and chest X-ray changes and lack of response to antibiotics or person visiting of residing in an area with recent SARS activity and with signs and symptoms of febrile respiratory disease and chest X-Ray changes and normal or decreased WBC count).
	Safety: N/A
Notes	Risk of bias: low
	Notes: the authors conclude that in virtue of the shape of the epidemic curve it is likely that the combination of measures taken before the 25th of April helped contain the spread of SARS. Although there may be alternative explanations this appears to be the most likely explanation of the facts. Hospitals were seen early on as sources of transmission of the SARS Co-V. The authors seem to doubt the direct effectiveness of entry port (for example, airports, stations, etc) checks (12 cases identified out of over 13 million people screened). They think screening was more useful to keep away sick people

Pelke 1994

Methods	Controlled before and after study conducted in a neonatal intensive care unit (NICU) of Kapiolani medical center, Honolulu, Hawaii, to assess the effect of gowning on RSV and other infections, on traffic and handwashing patterns. Alternate 2- months gowning and no- gowning cycles were established in a 24-bed NICU for 8 months. One entire 4-month cycle was repeated to eliminate the potential for seasonal variables and outbreaks. All the people entering into the NICU (physicians, nursing staff, ward clerks, families and visitors) wore gowns. During the no- gowning periods nursing staff wore hospital- issued pantsuit, washed at home through ordinary methods and worn from home. Ward clerks, physicians, hospital staff, families and visitors wore street clothes without gowns. Throughout the entire 8 month period, there was the recommendation for all staff and visitors to enforce initial 2 -minute hand scrub. Nails were cleaned before scrubbing, and a minimum 15-second hand wash between infants or equipment was expected. Surveillance cultures were done weekly on all patients. Without the knowledge of the NICU staff, a neonatal research nurse scheduled observations of traffic patterns, while ostensibly reviewing charts, to determine if a lack of gowning procedures encourage more traffic. Handwashing compliance was studied, again without staff awareness, by 30 minutes direct observation. Follow-up of infection rates was planned through standard infection control surveillance
Participants	230 infants, aged 22 to 42 weeks, with birth a weight of 464-6195 grams. Overall there were 330 infants admitted to NICU during the study period. Thus 17% of participants had no RSV cultures taken. The reasons given are vague (transfer or death)
Interventions	Use of gowns and standard procedures (handwashing) versus standard procedures
Outcomes	Laboratory: serological evidence: yes Effectiveness: RSV infection Safety: N/A
Notes	Risk of bias: medium (17% loss to follow up) Notes: the authors conclude that gowning did not protect NICU infants from any type of infection or affect mortality (1.21 versus 1.38/100 patient-days of gowning and no gowning periods respectively). Gowning procedures did not deter staff or visitors from entering the unit, since traffic was also unchanged between periods. Finally the results showed no change in handwashing patterns between periods. Besides the advantage of eliminating a potentially unnecessary ritual that may be perceived as a psychological barrier to families visiting their infants, other benefits to discontinuing gowning include saving staff tome involved in various gowning procedures and costs. If gowns are eliminated, it is recommended to perform careful follow up. The study conclusions must be taken with caution given the likely selection bias introduced by the missing 17% of children

Roberts 2000

Methods	Open cluster RCT carried out between March and November 1996 (the southern hemisphere winter season) in 23 child care centres caring for a minimum of 50 children 10 hours a day, 5 days a week in Australia. The study assessed the effects of an Australian national handwashing programme compared to standard procedure. Randomisation was according to a random number table and cluster coefficients are reported
Participants	Children (299 in the intervention arm and 259 in the control arm) aged 3 or younger attending the centres at least 3 days a week. Attrition was 51 children in the intervention arm and 72 children in the control arm due mainly to staff leaving the centres
Interventions	Handwashing programme with training for staff and children. It is unclear whether any extra hand cleansing agents were used, as GloGerm (?) is mentioned when it was used in a preliminary study
Outcomes	Laboratory: N/A

Roberts 2000 (*Continued*)

	Effectiveness: ARI (runny nose, cough and blocked nose) Follow up was via a parental phone interview every 2 weeks Safety: N/A
Notes	Risk of bias: low (cluster coefficients and analysis by unit of randomization Notes: The authors conclude that although there was no overall decrease in respiratory illness (RR 0.95 95% CI 0.89 to 1.01), but in children up to 24 months the decrease was significant (RR 0.90, 95% CI 0.83 to 0.97). The authors speculated that this was because maximum benefits are likely from this age group because of their limited ability to wipe their nose and hands without a structured programme. Analyses by three compliance levels are also reported. A so-so reported and well conducted trial

Ryan 2001

Methods	Retrospective and prospective controlled before and after study carried out at the US Navy's Great Lakes recruit training centre, in Illinois. Rates of respiratory disease were retrospectively calculated for recruits undergoing training for 3 periods: 1996, before the implementation of "Operation Stop Cough" and 1997 and 1998. To compare rates of respiratory illness with a similar community the authors also looked at the incidence of respiratory illness in a population of phase II sailors undergoing the second part of their training in the same camp. In addition a compliance questionnaire was also carried out during the latter two years of the study
Participants	Recruits undergoing training (44,797 in 1996; 47,300 in 1997; and 44,128 in 1998) mainly men, aged around 19 to 20 and a control population of phase II training sailors (no precise denominators given but around 10,000 yearly) who did not have a programme of hand washing
Interventions	Structured top-down programme of handwashing at least 5 times daily
Outcomes	Laboratory: N/A Effectiveness: respiratory illness detected from sick parade records and outgoing recruits questionnaire on a sample survey Safety: N/A
Notes	Risk of bias: low Notes: the authors conclude that implementation of the control programme has seen near-halving of incidence of ARIs (based on three stratified samples of recruits infrequent hand washers had more self reported episodes of ARIs (4.7 versus 3.2 per recruit, OR 1.5, 95% CI 1.2 to 1.8) and reported more hospitalisations (OR 10.9, 95% CI 2.7 to 46.2). Despite dramatic results, implementation was and continues to be difficult

Sandora 2005

Methods	Single-blind cluster randomised controlled trial carried around the Boston area, USA, in the period November 2002 to April 2003. The trial tested the effects of using a hand sanitiser and a programme of instruction on the transmissions of GI infections (data not extracted) and ARIs in families. Units of randomisation were child care centres and were carried out on enrolment by an investigator using random block size generated by computer. Assignment was single blind (i.e. investigator blinded to the status of the centre). Cluster correlation was 0.01
Participants	292 families with 1 or more children aged 6 months to 5 years who were in child care for 10 or more hours a week. There were 155 children in 14 centres allocated to the intervention arm and 137 children in 12 centres allocated to

Sandora 2005   (*Continued*)

	the control arm. The mean age was 3 to 2.7 years. Attrition was respectively 15 (3 lost to follow up and 12 who discontinued the intervention) and 19 (8, lost to follow up and 11 who discontinued the intervention). ITT analysis was carried out
Interventions	Alcohol-based hand sanitiser with bi-weekly hand-hygiene educational materials over 5 months versus bi-weekly educational material on healthy diet
Outcomes	Effectiveness: ARI (two of the following symptoms for 1 day or 1 of the following symptoms for 2 days: runny nose, cough, sneezing, stuffy or blocked nose, fever, sore throat). An illness episode had to be separated by 2 symptom-free days from a previous episode. A secondary illness was when a it followed a similar illness in another family member by 2 to 7 days Follow up was by means of bi-weekly phone calls to care givers Safety: dry skin (71 reports), stinging (11 reports), bad smell (7 reports), dislike (2 reports), allergic reaction (2 reports), slippery feel (1 report) and irritation (20 reports)
Notes	Risk of bias: low Notes: the authors conclude that although the rate of GI illnesses was significantly lower in the intervention group, the incidence rate ratio - IRR was not significantly different for ARIs (0.97; 95% CI 0.72 to 1.30). Compliance and droplet route spread may account for this apparent lack of effect. A well reported trial

Seto 2003

Methods	Case-control study Hong Kong, China, conducted during the period 15 march to 24 March 2003 in five hospitals. The study aims were to assess the effectiveness of protective procedures for contracting SARS in HCWs exposed to 11 index cases in three of the five hospitals during the SARS epidemic
Participants	Description of cases: 13 HCWs infected with confirmed SARS within 2 to 7 days of exposure with no community exposure, 4 males and 9 females 2 doctors, 6 nurses, 4 healthcare assistants and 1 domestic staff who came into contact with SARS index cases. Only one used no protection measures and all omitted at least one of the protective measures required (handwashing, masks, gloves, gowns). Cases were identified through notification, which has been active since early February. A SARS cases was defined as having fever of 38 C or more, radiological infiltrates, and two of either: new cough, malaise, signs of consolidation Description of controls: 241 staff from the five hospitals who were not infected. The authors report that use of measures was elicited using questionnaires, 365 of which were returned (85% response rate). Non responders were likely to be on leave or night shift. Data for 102 staff were excluded because they had no exposure to SARS
Interventions	Exposure was defined as coming within 0 to 91 metres (3 feet) of an index case with SARS symptoms when providing care. Recommended measures were handwashing, masks, gloves and gowns
Outcomes	SARS
Notes	Risk of bias: medium (inconsistencies in the text: lack of description of controls) Notes: The authors conclude that the 69 staff reporting use of all 4 measures were not infected, whereas all infected staff had omitted at least one measure. Simple analysis showed that masks, gowns and handwashing (OR 5, 95% CI 1 to 19) were effective but only masks (OR 13, 95% CI 3 to 60) were significant at logistic regression, possibly through lack of power. No blind assessment of cases and control data was carried out and 15% attrition of questionnaires may have introduced bias. The study was published as research letter in the Lancet, so possible lack of space may have affected reporting clarity

Simon 2006

Methods	Controlled before and after study to assess the effects of a programme to prevent transmission of nosocomially acquired RSV (RSV) infections in hospitalized patients. The study describes "a specialized database for surveillance" in a university children's hospital in Bonn, Germany. The study took place between 1999 and 2002 (three seasons each starting November 1 and finishing April 30) and the incidence of RSV nosocomially acquired infections for the first season was compared to those of the second and third seasons
Participants	The denominator was all paediatric in-patients with a diagnosis of RSV admitted for at least 24 hours (283 RSV infections in the 278 general - i.e. with and without risk factors for RSV - hospitalised people in total). As these were reported broken down by season data were extracted only for admissions. The numerator was 39 cases (13.8%) which were nosocomial infections (24, 13 and 2 respectively in each of the seasons). Nearly forty-nine percent of all nosocomial infections were found in prematurely born infants. Mean age of participants was 12 months. Other important data are reported (e.g. birth weight, length of stay and duration of viral shedding but without before and after breakdown). In prematurely born infants however the text reports 19 infections: 12 in 99-00, 7 in 00-01 and 0 in 01-02 (this contradicts the data in table 1, where 19 term infants had nosocomial infections, meaning the remaining 20 were premature)
Interventions	Multifaceted barrier concept (enhanced surveillance and feedback, rapid diagnosis, barriers and isolation, disinfection of surfaces) based on the CDC recommendations introduced in September 2000
Outcomes	Laboratory: quick and full pathogen identification with antigen detection Effectiveness: RSV nosocomial infection (RSV positive patient becoming symptomatic on day 5 or later since admission). Illness severity also defined but the data were not extracted
Notes	Risk of bias: low Notes: Following the introduction of the surveillance and prevention policy, a 9-fold decrease (1.67 vs. 0.18/1000 patient-days) was found when comparing the first and the last season. Intensive care treatment was required in 18% of all documented RSV-infections, in 48.7% of all NI cases and in 43.5% of all RSV-infected prematurely born infants. Overall RSV-related mortality was 0.71%. The authors conclude that early diagnosis, a strict cohorting and contact isolation policy, and prospective surveillance contribute to the reduction of nosocomial RSV infection. A reasonably reported study with incidence data presented by sex, age group, birth weight etc in an attempt to minimise bias

Snydman 1988

Methods	Controlled before and after study conducted during the winters of 1983-84 (retrospectively), 1984 to 1985 and 1985 to 1986 (prospectively) to assess whether the introduction of infection control measures halted transmission of RSV in a special nursery in Boston USA. Record review for the retrospective part and prospective study for the two seasons following the introduction of infection control measures
Participants	HCW and patients in the special care baby unit
Interventions	From the 1984 to 1985 season the following were introduced: Active surveillance Extensive cohorting of patients and staff Respiratory precautions on suspicion of respiratory case Gown, mask and gloves used on contact Restricted visiting policy Segregation of cases
Outcomes	Laboratory: RSV culture

Snydman 1988 (*Continued*)

	Effectiveness: RSV cases with symptoms and laboratory confirmation Safety: N/A
Notes	Risk of bias: high Notes: The authors conclude that there were 7 cases in the season "before" and no cases in the following seasons (no transmission per 1000 patient days in the post-intervention period compared 8 per 1000 patient days in the pre-intervention period). No denominators are provided (hence no data can be extracted) and exposure is generically quantified by aggregate patient- days of exposure. It is unclear how the circulation of RSV outside related to the claimed success of the measures, as no information is provided

Somogyi 2004

Methods	Prospective cohort study of 9 observation (3 each when using 3 different masks). The authors observed and photographed droplet dispersal while a volunteer breathed out 3 times in 3 different types of mask
Participants	1 volunteer
Interventions	Three masks, two without air filter and allowing external exhalation, one with manifold and air filter
Outcomes	Effectiveness: plume of droplets as observed and photographed: masks were poor at preventing droplet spread
Notes	Risk of bias: low Notes: the authors conclude that the mask with manifold and air filter did not allow dispersal of droplets and was far safer in an epidemic such as SARS to contain the spread. Simple, safe and effective study

Teleman 2004

Methods	Case-control study assessing risk and protective factors in HCWs during the SARS outbreak in Singapore (1 to 22 March 2003)
Participants	Description of cases: 36 HCWs admitted with probable SARS (according to WHO definition) during 1 to 31 March 2003. Six others were too ill to speak and 2 others died Description of controls: 50 HCWs working on the same wards who had definite exposure to SARS (physical proximity of 1 metre or less of a patient subsequently diagnosed as having SARS) but did not develop SARS
Interventions	Data on personal details and symptoms and exposure were gathered via a closed phone questionnaire. The 2 groups were comparable for demographic and epidemiological characteristics except that non-Chinese ethnic groups were twice as common among controls The following risk factors were assessed: Distance from source of infection < 1 meter Duration of exposure 60 or more minutes Wearing N95 mask Wearing gloves Wearing gown Touched patients Touched patients' personal belongings Contact with respiratory secretions

Teleman 2004   (*Continued*)

	Performed venepuncture Performed or assisted in intubation Performed suction of body fluids Administered oxygen Hand washing after each patient
Outcomes	SARS
Notes	Risk of bias: low Notes: The authors conclude that three factors were associated with significant risks or protection: Wearing N95 mask OR 0.1 (95% CI 0.02 to 0.86) Contact with respiratory secretions OR 21.8 (95% CI 1.7 to 274.8) Hand washing after each patient OR 0.07 (95% CI 0.008 to 0.66) A well reported study, let down by the failure to indicate whether assessment of risk factors had been carried out blindly to cases or control status. I wonder how much of the non-significance for certain factors is due to lack of statistical power

Turner 2004a

Methods	Double-blind randomised controlled trial conducted by Hill Top Research, Inc. Winnipeg, Canada, to assess the efficacy of acids with virucidal activity for the inactivation of virus and prevention of experimental Rhinovirus colds. Subjects in good health, aged 18 to 60, were recruited from Winnipeg and surrounding communities for participation. Qualified subjects were randomised to treatment with vehicle (62% ethanol, 1% ammonium lauryl sulfate, and 1% Klucel), vehicle containing 3,5% salicylic acid or vehicle containing 1% salicylic acid and 3,5% pyroglutamic acid. The volunteers' hands were disinfected and then test product was applied to both hands of each subject. Fifteen minutes after application, the fingerprints of each hand were contaminated with Rhinovirus type 39. The volunteers touched conjunctiva and the nasal mucosa only with the right hand. Viral contamination of the fingers was assessed in the left hands of the volunteers, and viral infection was assessed by culture of nasal lavage specimens and blood samples
Participants	85 volunteers, 31 control group, 27 used vehicle with 3.5% salicylic acid, 27 used vehicle with 1% salicylic acid and 3.5% pyroglutamic acid
Interventions	Use of salicylic acid versus salicylic acid and pyroglutamic acid versus "placebo" substance
Outcomes	Laboratory: yes Effectiveness: rhinovirus type 39 infection Safety: N/A
Notes	Risk of bias: high (no description of randomization process, concealment, or allocation) Notes: the authors concluded that organic acids commonly used in over-the-counter skin care and cosmetic products have substantial virucidal activity against rhinovirus. These preparations provided effective residual antiviral activity on the hands. The virucidal effect of these hand treatments resulted in a reduction in the incidence of rhinovirus infection in the treated volunteers (P = 0.025). The utility of this observation in the natural setting remains to be determined. The volunteers were not allowed to use their hands in the interval between the hand treatment and the virus challenge, so the effect of normal use of the hands on the virucidal activity of these organic acids is not known. Similarly, the virus challenge method used in these experiments may not simulate the natural setting in all aspects. The effect of nasal secretions that would be transferred with the virus in the natural setting on the activity of the acids or on the transmission of virus was not tested in the model. We are unsure as to the practical significance of this study and the generalisability of its results to the real world. Poorly reported study

Turner 2004b

Methods	Double-blind randomised controlled trial conducted by Hill Top Research, Inc. Winnipeg, Canada, to assess the residual virucidal activity of a skin cleanser wipe and its effectiveness in preventing experimental Rhinovirus colds. Subjects in good health and from 18 to 60 were recruited from Winnipeg and surrounding communities for participation.
	The residual activity of a skin cleanser wipe containing 4% pyroglutamic acid formulated with 0.1% benzalkonium chloride was tested. The negative control treatment was 62% ethanol. Benzalkonium chloride had been previously tested and was found to have no virucidal activity. Volunteers were randomly assigned to use the control preparation or the active preparation. The study material was applied to hands with a towelette. Fifteen minutes later, when the fingers were completely dry, the fingertips of each hand of the control subjects and the volunteers in the active treatment group were contaminated with Rhinovirus type 39. An additional volunteer in the active group were challenged with virus 1 hour after application and the final group of volunteers was challenged 3 hours after application. Viral infection was assessed by culture of nasal lavage specimens and blood samples
Participants	122 volunteers, 30 control group, 92 active group (30 tested after 15 minutes, 30 after 1 hour, 32 after 2 hours)
Interventions	Use of a skin cleanser wipe containing 4% pyroglutamic acid formulated with 0.1% benzalkonium chloride versus skin cleanser wipe containing ethanol
Outcomes	Laboratory: yes
	Effectiveness: rhinovirus type 39 infection
	Safety: N/A
Notes	Risk of bias: high (no description of randomisation process, concealment, or allocation)

White 2001

Methods	Double blind placebo-controlled cluster randomised trial that took place in 3 schools in California during March to April 1999. The study assessed the incremental value of using an alcohol hand rub together with water & soap handwashing. Both arms had been given an educational programme starting 2 weeks prior to the beginning of the trial. Randomisation was by classroom and the placebo hand rub was indistinguishable from the active ingredient. Details of randomisation are not given
Participants	Of the 72 classes originally recruited, lack of compliance (use of supplementary product at least 3 times a day), reduced the classes to 32 (16 in both arms) with 769 participants aged 5 to 12
Interventions	Pump activated antiseptic hand rub with benzalkonium chloride (SAB) (Woodward Laboratories) or inert placebo that "virtually" looked the same in batches of four colour coded bottles containing both. School staff, parents and participants were blinded
Outcomes	Laboratory: testing of virucidal and bactericidal activity of the active compound
	Effectiveness: ARI (cough, sneezing, sinus trouble, bronchitis, fever, red eye, headache, mononucleosis, acute exacerbations of asthma)
	Gastrointestinal and other illnesses (data not extracted)
	Follow up and observation was carried out by classroom staff and illnesses were described by parents
	Safety: 7 students dropped out because of mild sensitivity to the rub
Notes	Risk of bias: high (no description of randomisation; partial reporting of outcomes, numerators and denominators)
	Notes: the authors conclude that addition of the rub led to a 30 to 38% decrease of illness and absenteeism (RR for illness absence incidence 0.69, RR for absence duration 0.71). Very high attrition, unclear randomisation procedure, educational programme and use of placebo hand rub make generalisability of the results debatable. No confidence

White 2001 (*Continued*)
                               intervals reported

White 2003

Methods	Prospective open cohort study carried out at the university of Colorado Boulder campus during eight weeks in the autumn-winter of 2002. The study aimed at assessing the effects of hand hygiene on URTIs and absenteeism. Allocation was by residence hall with 2 halls doing "knowledge studies" being allocated, one to each arm
Participants	430 students aged around 18 mainly females were recruited but only 188 in the intervention cluster and 203 in the control cluster completed at least 3 weeks' follow up. Students were recruited with cash incentives. No reasons for attrition are given
Interventions	Education programme and alcohol gel adjunct to handwashing in residence halls versus standard hygiene
Outcomes	Laboratory: in vitro testing of the antibacterial and antiviral properties of the hand rub Effectiveness: URTI (at least 2 symptoms with one of them lasting at least 2 to 3 days. List of symptoms as follows: sore throat, stuffy nose, ear pain, painful/swollen neck, cough, chest congestion, sinus pain, fever, working days lost). Weekly surveys were carried out before during and after the study Safety: N/A
Notes	Risk of bias: medium Notes: the authors conclude that the intervention resulted in significantly fewer symptoms (reductions of 14.8% to 39.9 %) and absenteeism (40% reduction). Unexplained attrition and unknown effect of cash incentives. Relatively unclear definition of illness with a hint of a sensitivity analysis in the footer to a table

Wu 2004

Methods	Case-control study carried out on the Beijing SARS outbreak to assess the reasons for the insurgence of SARS cases in people who had no apparent contact with a SARS case
Participants	Description of cases: 94 probable or suspected SARS cases (Ministry of Health of China definitions) hospitalised during the period 28 April 2003 to 9 June 2003, aged 14 or more and non-HCWs with no known or reported no close contact with probably or suspected SARS cases. Fifty percent of cases were males with a median age of 29 years. The definition changed after 3 May to include those with symptoms who travelled to or resided in areas with known recent SARS activity but did not necessarily have contact with an index case. No laboratory confirmation of SARS was included in the definition which was purely practical (i.e. clinical-anamnestic). However antibody titres were taken several weeks after symptoms had abated. Close contacts (which played a part in the earlier case definition) were defined as persons who shared utensils, meals, residence hospital room or transportation vehicle with a suspected SARS or those who visited or came into contact with body fluids up to 14 days prior to the development of the index case's symptoms. Cases and controls were interviewed during the period 3 to 16 June Description of controls: 281 controls selected each by telephone random number change of last digits of the cases' phone numbers. This was aimed at providing neighbouring matching. Controls were interviewed by 4 July 2003. Seven controls (two matched sets) were excluded because they were aged less than 14 and seven matched sets were excluded because the case was reclassified as a HCW Cases and controls were interviewed for the 2 weeks preceding symptoms
Interventions	Always wearing a mask

Wu 2004 (*Continued*)

    Intermittently wearing a mask
    Washing hands
    Owning a pet
    Visiting a farmer's market
    Visited clinics, eaten out, or taken taxis

Outcomes	SARS
Notes	Risk of bias: medium (inconsistencies in the text: lack of description of controls) Notes: The authors conclude that cases were more likely than controls to have chronic pathologies (OR 4.1 95% CI 1.8 to 9.3) or have visited fever clinics (OR 13.4 95% CI 3.8 to 46.7), eaten out (OR 2.3 95% CI 1.2 to 4.5) or taken taxis more than once a week (OR 3.2 95% CI 1.3 to 8.0). In other words, unrecognised sources of transmission were present in the community. Always wearing a mask use was strongly protective (70% reduction in risk, OR 0.3 95% CI 0.2 to 0.7) and even wearing one intermittently with a smaller significant reduction in risk (OR 0.5 95% CI 0.2 to 0.9) and so was always washing hands after returning home (OR 0.3 95% CI 0.2 to 0.7) and owning a pet (OR 0.4, 95% CI 0.2 to 0.9) and visiting a farmer's market (OR 0.4 95% CI 0.2 to 0.8). Of great interest is the role of fever clinics in spreading the disease, probably because of poorly implemented isolation and triage procedures. A fascinating study

Yen 2006

Methods	Retrospective cohort study carried out during 27 April to 21 May 2003 in one military hospital in Taiwan, China (intervention hospital) and 86 control hospitals. The study aims were to assess the effectiveness of an integrated infection control policy introduced in the intervention hospital in protecting HCWs and patients from SARS infection
Participants	85 doctors, 203 nurses and 171 administrative staff and volunteers in the intervention hospital and an unknown number of their colleagues in the 86 control hospitals (746 high risk infectious disease beds)
Interventions	Integrated infection-control strategy with triage and barriered traffic flow into hospital, risk zoning, negative pressure areas of isolation, personal hygiene and barrier interventions versus normal isolation procedures
Outcomes	Laboratory: for confirmation of SARS Co-V Effectiveness: SARS cases probable or suspect (WHO case definitions) Safety: N/A
Notes	Risk of bias: high Notes: the authors conclude that during the study period only 2 HCWs were infected with SARS but there were 43 suspected and 50 probable cases in the control hospital. The difference was statistically significant. Sketchily reported study with missing denominators and data on exposure to SARS, as one would expect from a study carried out during an epidemic. I am not clear how the intervention differed from high risk isolation procedures

Yin 2004

Methods	Case-control study carried out in ten hospitals of Gunandong province, China, comparing the rate of usage of protective measures in HCWs with SARS and without SARS. The rate of exposure to SARS between two groups was similar. The data were obtained by questionnaire. Limited information is available from the abstract and from partial translation of the original text in Chinese

Yin 2004 (*Continued*)

Participants	Description of cases: 77 HCWs who had contracted SARS
	Description of controls: 180 HCWs who had not contracted SARS
	Both cases and controls had been working in isolation units and took part in delivering first aid and caring for SARS patients. No significant differences were noted between cases and controls for a series of variables
Interventions	Mouth mask
	Thick mouth mask (more than 12 layers of cloths)
	Use one-off paper mouth mask
	Never use mouth mask
	Wear eye mask if necessary
	Protecting for nose and eyes mucosa
	Wear shoe gloves
	Wear barrier gown
	Wear hand gloves
	Rinse out mouth
	Take bath and change clothes before home
	Check mouth mask
	Intake oseltamivir phosphate orally
	Never eating and smoking in the ward
	Hand washing and disinfection
	Using nose clamp
	Intake herbal Banlangen (Indigowoad Root) orally
Outcomes	SARS
Notes	Risk of bias: medium (inconsistencies in the text: lack of description of controls)
	Notes: the authors conclude that the combination of mouth mask, barrier gown, gloves, goggles, footwear, rinse out mouth and take bath and change clothes before provided significant protection and that there was a dose-response relation with the more interventions used in combination the better the protection. Single measures such as wearing of a mask (OR 0.78 95% CI 0.60 to 0.99), goggles (OR 0.20, 95% CI 0.10 to 0.41) and footwear (OR 0.58 95% CI 0.39 to 0.86) were effective
	Limited information is available from the abstract and from partial translation of the original text in Chinese

HCW: health care worker
CXR: chest X-ray
RSV: respiratory syncytial virus
URTI: upper respiratory tract infection
OR: odds ratio
Hanoi French Hospital (HFH)
ITT: intention-to-treat
GI: gastro-intestinal
SCBU: special care baby unit
WBC: white blood cell
NICU: neonatal intensive care unit

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abou El Hassan 2004	Topic completely extraneous
Amirav 2005	Randomised controlled trial of aerosol treatment
Anderson 2004	Mathematical model with interesting discussion of interaction between public health measures
Anonymous 2002	News item
Anonymous 2003	No data presented
Anonymous 2004	News item
Anonymous 2005a	News item
Anonymous 2005b	News item
Anonymous 2005c	News item
Aragon 2005	Descriptive paper (non-comparative). Has no viral outcomes
Barros 1999	Correlational study between incidence of upper respiratory tract infection (URTI) and factors such as overcrowding
Bell 2004	Has unpublished entry exit screening data and extensive references but no comparative data
Ben-Abraham 2002	Exclude - bacterial illness only
Black 1981	Diarrhoea only outcome
Breugelmans 2004	Description of risk factors in aircraft
Carter 2002	News item
Castillo-Chavez 2003	Editorial
Cava 2005a	Survey of quarantinees' views
Cava 2005b	Personal experiences of quarantine
CDC 2003	Case reports
Chai 2005	Letter - about MRSA
Chaovavanich 2004	Case report
Chau 2003	No original retrievable data. Mathematical model fitting expected to observed cases with quarantine in the SAR of Hong Kong
Chia 2005	Knowledge survey
Davies 1994	Antibody titres as outcomes with so many biases that interpretation of study is problematic
Day 1993	No acute respiratory infection outcome data

(*Continued*)

Study	Reason for exclusion
Day 2006	Mathematical model no new data
Dell'Omodarme 2005	Probabilistic and Bayesian mathematical model of screening at entry
Desenclos 2004	Description of transmission
DiGiovanni 2004	Qualitative study of compliance factors in quarantine
Doebbeling 1992	RCT respiratory data not present. Only 3 viruses isolated in total with no viral typing available
Dwosh 2003	Case series
Fendler 2002	Cohort study badly biased with differential health profiles and healthcare workers dependency in intervention and control semi-cohorts. No attempt at adjusting for confounders was made. No denominators available
Flint 2003	Description of spread in aircraft and non-comparative data
Fung 2004	Non-comparative
Gaydos 2001	Editorial linked to Ryan
Gensini 2004	Interesting historical review
Giroud 2002	Non clinical outcomes
Glass 2006	Mathematical model - no original data presented
Gore 2001	Summary of Dyer 2000 (already included)
Gostin 2003	Not an analytical study
Guinan 2002	It would appear that nine classes took part and "acted as their own controls", but it is not clear if there was crossover of classes or not. In addition the outcome is combined gastrointestinal/respiratory. The clue lies in the presence of a nested economic analysis which shows considerable savings in time for staff and pupils is the soap is used: in other words this is a (covert) publicity study
Gupta 2005	Economic model - no new data
Gwaltney 1982	No breakdown of cases by arm given
Han 2003	Non-comparative
Hayden 1985	This is an RCT with laboratory induced colds, small numbers uncertain numerators but almost certainly because of the unique laboratory conditions (placebo tissues not being a placebo at all) of impossible generalisation. It was a pilot to the far bigger trial by Farr et al (included)
Hendley 1988	Inappropriate intervention
Hilburn 2003	No ARI/viral outcomes (e.g. URTIs)
Ho 2003	Descriptive review
Jiang 2003	Two papers probably the same paper in different versions: Jiang SP, Huang LW, Wang JF, Wu W, Yin SM, Chen WX, et al. [A study of the architectural factors and the infection rates of healthcare workers in isolation units for severe acute respiratory syndrome]. [Chinese] Chung-Hua Chieh Ho Ho Hu Hsi Tsa Chih [Chinese Journal of Tuberculosis & Respiratory Diseases]. 26(10):594-7, 2003 Oct
Jones 2005	Historical account
Kaydos-Daniels 2004	Not an analytical study
Kosugi 2004	Non-comparative study

Lam 2004	Outcomes were generic (infection rates). No laboratory data available for viral diagnosis
Lange 2004	No data presented
Larson 2004	Inappropriate outcomes
Larson 2005	Cluster RCT comparing the effects of 2 hand hygiene regimens on infection rates and skin condition and microbial counts of nurses' hands in neonatal intensive care units. Outcomes were generic (for example, pneumonia and microbial counts of participants' skin). No laboratory data available for viral diagnosis
Lau 2004b	Attitude survey
Lau 2005	Herbal remedy effectiveness assessment
Lee 2005	Descriptive study of risk and protective factors of transmission in households. No assignment took place
Lipsitch 2003	Mathematical model fit to evidence
Luckingham 1984	Historical report on Tucson experience during Spanish flu pandemic
Ma 2004	Case-control study of risk factors for SARS
Marin 1991	Viral resistance study
Monsma 1992	Non-comparative study
O'Callaghan 1993	Letter linked to Isaacs 1991
Olsen 2003	Description of transmission
Ooi 2005	Descriptive study but with interesting organisational chart
Pang 2004	Descriptive study of Beijing outbreak. Some duplicate data in common with Pang 2004
Pittet 2000	Analysis of relationship between handwashing compliance campaign and nosocomial bacterial infections (e.g. MRSA)
Prasad 2004	Letter of retrospective cohort - behavioural
Rabenau 2005	In vitro test of several disinfectants
Riley 2003	Mathematical model fit to evidence
Rosenthal 2005	Outcomes were generic (for example, pneumonia, URTIs). No laboratory data available for viral diagnosis
Safiulin 1972	Non-comparative set of studies with no clinical outcomes
Satter 2000	Experiment assessing virucidal activity of finger tip surface - no clinical outcome data
Sizun 1996	This is a review, with no original data presented
Svoboda 2004	Descriptive study with before and after data but shifting denominators
Ueno 1990	Experimental study. No clinical intervention
Wang 2003	Descriptive study
Wang 2005	Case-control study of susceptibility factors
Weber 2004	Editorial linked to Larson 2004
White 2005	Redundant publication of White 2003

(*Continued*)

Study	Reason for exclusion
Wilczynski 1997	Clinical trial of the effects of breast feeding
Wilder-Smith 2003	Description of risk factors in aircraft
Wilder-Smith 2005	Descriptive review
Wong 2005	Attitude survey
Yu 2004	Description of transmission
Zamora 2006	Head-to-head comparison of two sets of PPEs with no controls and no clinical outcomes
Zhao 2003	CCT of SARS treatment

DATA AND ANALYSES

Comparison 1. Case control studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Thorough disinfection of living quarters	1	990	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.23, 0.39]
2 Frequent handwashing	6	2077	Odds Ratio (M-H, Fixed, 95% CI)	0.45 [0.36, 0.57]
3 Wearing mask	5	1991	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.25, 0.40]
4 Wearing N95 mask	2	340	Odds Ratio (M-H, Fixed, 95% CI)	0.09 [0.03, 0.30]
5 Wearing gloves	4	712	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.29, 0.65]
6 Wearing gowns	4	712	Odds Ratio (M-H, Fixed, 95% CI)	0.23 [0.14, 0.37]
7 All interventions	2	369	Odds Ratio (M-H, Fixed, 95% CI)	0.09 [0.02, 0.35]

Analysis 1.1. Comparison 1 Case control studies, Outcome 1 Thorough disinfection of living quarters.

Review: Interventions for the interruption or reduction of the spread of respiratory viruses

Comparison: 1 Case control studies

Outcome: 1 Thorough disinfection of living quarters

Study or subgroup	Cases n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Lau 2004a	154/330	492/660		100.0 %	0.30 [0.23, 0.39]
Total (95% CI)	**330**	**660**		**100.0 %**	**0.30 [0.23, 0.39]**

Total events: 154 (Cases), 492 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 8.51 (P < 0.00001)

0.1   1   10

Favours disinfection   Favours control

Analysis 1.2. Comparison 1 Case control studies, Outcome 2 Frequent handwashing.

Review: Interventions for the interruption or reduction of the spread of respiratory viruses

Comparison: 1 Case control studies

Outcome: 2 Frequent handwashing

Study or subgroup	Cases n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Lau 2004a	61/330	222/660		57.3 %	0.45 [0.32, 0.62]
Nishiura 2005	15/25	56/90		4.6 %	0.91 [0.37, 2.25]
Seto 2003	10/13	227/241		2.5 %	0.21 [0.05, 0.83]
Teleman 2004	27/36	46/50		4.6 %	0.26 [0.07, 0.93]
Wu 2004	73/94	253/281		13.4 %	0.38 [0.21, 0.72]
Yin 2004	28/77	97/180		17.6 %	0.49 [0.28, 0.85]
Total (95% CI)	**575**	**1502**		**100.0 %**	**0.45 [0.36, 0.57]**

Total events: 214 (Cases), 901 (Control)

Heterogeneity: Chi^2 = 4.58, df = 5 (P = 0.47); I^2 =0.0%

Test for overall effect: Z = 6.56 (P < 0.00001)

```
        0.1          1        10
    Favours handwashing    Favours control
```
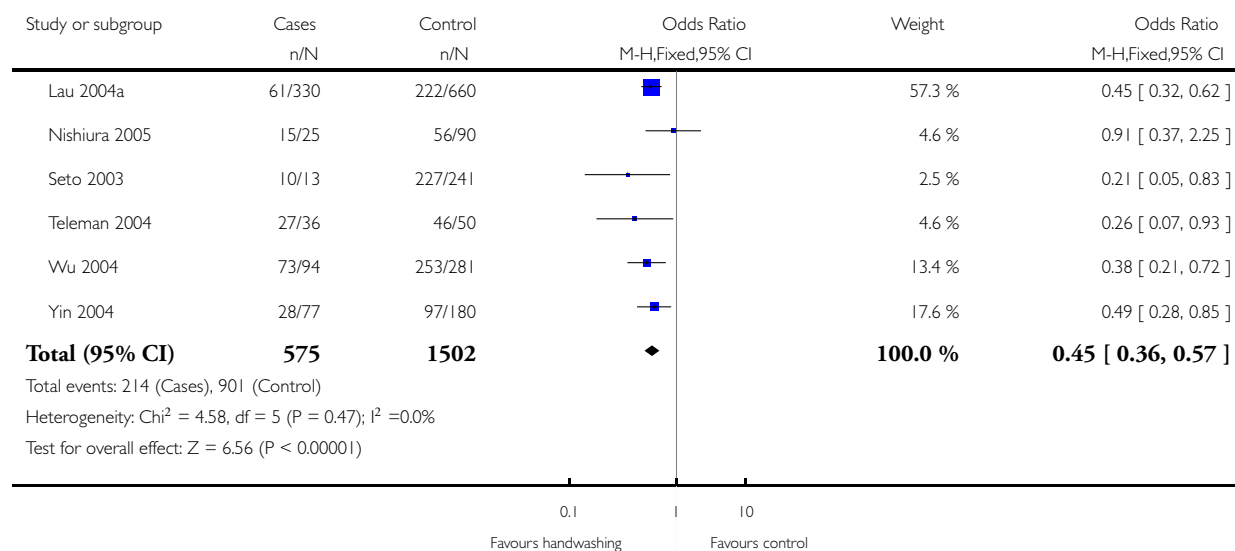
Analysis 1.3.   Comparison 1 Case control studies, Outcome 3 Wearing mask.

Review: Interventions for the interruption or reduction of the spread of respiratory viruses

Comparison: 1 Case control studies

Outcome: 3 Wearing mask

Study or subgroup	Cases n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Lau 2004a	93/330	388/660		71.9 %	0.28 [0.21, 0.37]
Nishiura 2005	8/25	35/90		4.0 %	0.74 [0.29, 1.90]
Seto 2003	0/13	51/241		2.1 %	0.14 [0.01, 2.34]
Wu 2004	25/94	121/281		17.2 %	0.48 [0.29, 0.80]
Yin 2004	68/77	178/180		4.8 %	0.08 [0.02, 0.40]
Total (95% CI)	**539**	**1452**		**100.0 %**	**0.32 [0.25, 0.40]**

Total events: 194 (Cases), 773 (Control)

Heterogeneity: Chi² = 9.62, df = 4 (P = 0.05); I² =58%

Test for overall effect: Z = 9.52 (P < 0.00001)

```
        0.1          1      10
    Favours masks      Favours control
```

Analysis 1.4.   Comparison 1 Case control studies, Outcome 4 Wearing N95 mask.

Review: Interventions for the interruption or reduction of the spread of respiratory viruses

Comparison: 1 Case control studies

Outcome: 4 Wearing N95 mask

Study or subgroup	Cases n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Seto 2003	0/13	92/241		35.6 %	0.06 [0.00, 1.02]
Teleman 2004	3/36	23/50		64.4 %	0.11 [0.03, 0.39]
Total (95% CI)	**49**	**291**		**100.0 %**	**0.09 [0.03, 0.30]**

Total events: 3 (Cases), 115 (Control)

Heterogeneity: Chi² = 0.14, df = 1 (P = 0.70); I² =0.0%

Test for overall effect: Z = 3.89 (P = 0.000098)

```
      0.01    0.1    1    10   100
    Favours N95 masks    Favours control
```

Analysis 1.5.   Comparison 1 Case control studies, Outcome 5 Wearing gloves.

Review: Interventions for the interruption or reduction of the spread of respiratory viruses

Comparison: 1 Case control studies

Outcome: 5 Wearing gloves

Study or subgroup	Cases n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Nishiura 2005	8/25	30/90		12.2 %	0.94 [0.36, 2.43]
Seto 2003	4/13	117/241		11.4 %	0.47 [0.14, 1.57]
Teleman 2004	10/36	22/50		18.3 %	0.49 [0.20, 1.23]
Yin 2004	37/77	136/180		58.2 %	0.30 [0.17, 0.52]
Total (95% CI)	**151**	**561**		**100.0 %**	**0.43 [0.29, 0.65]**

Total events: 59 (Cases), 305 (Control)

Heterogeneity: Chi^2 = 4.33, df = 3 (P = 0.23); I^2 =31%

Test for overall effect: Z = 4.07 (P = 0.000046)
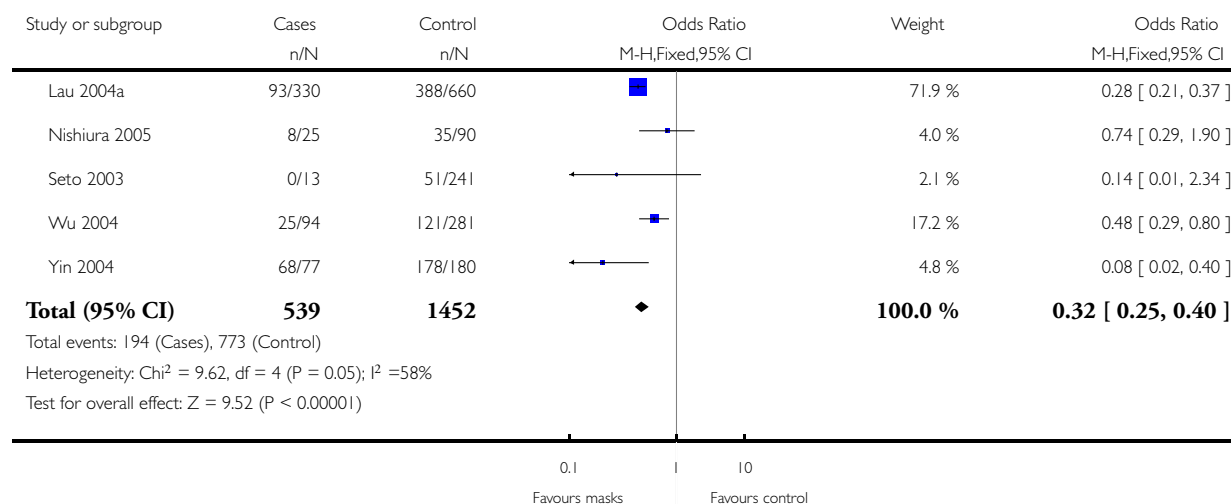
0.1   1   10

Favours gloves   Favours control

Analysis 1.6.   Comparison 1 Case control studies, Outcome 6 Wearing gowns.

Review: Interventions for the interruption or reduction of the spread of respiratory viruses

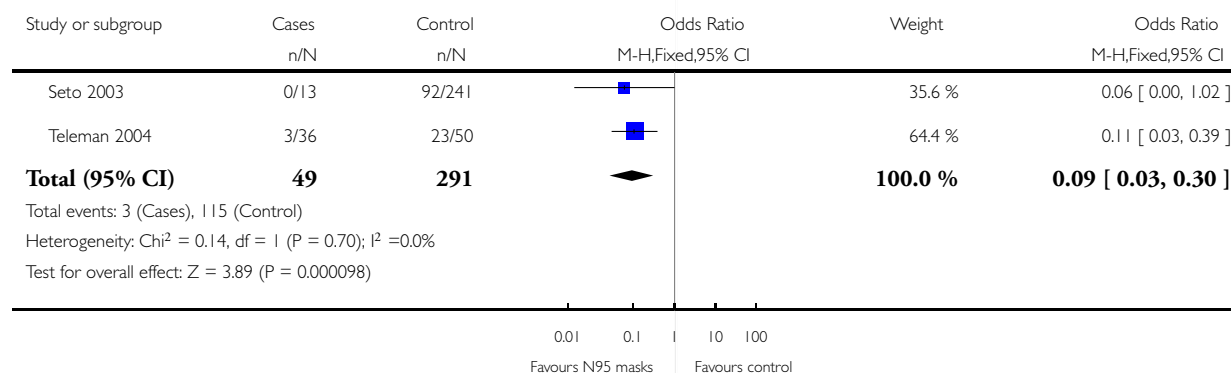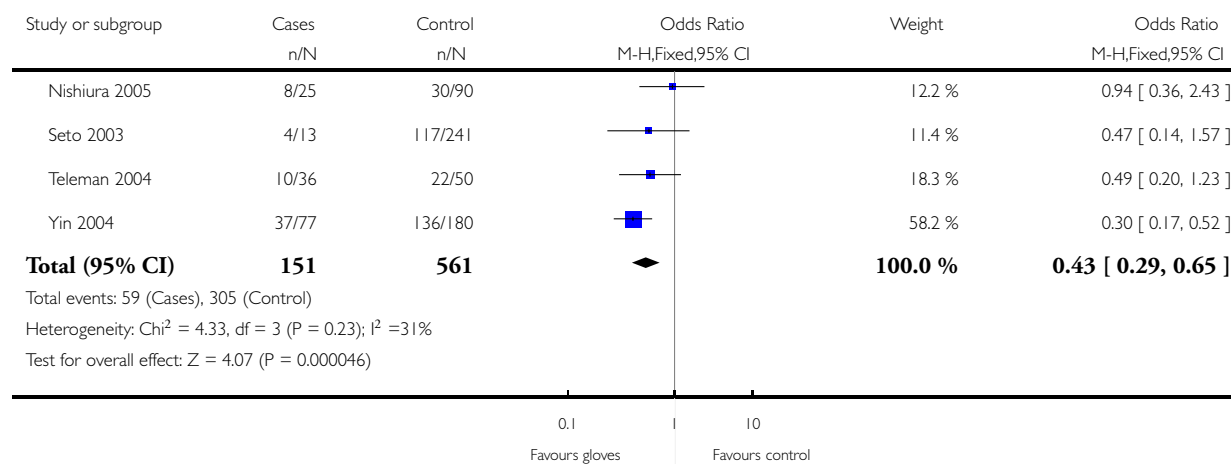Comparison: 1 Case control studies

Outcome: 6 Wearing gowns

Study or subgroup	Cases n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Nishiura 2005	2/25	25/90		12.8 %	0.23 [0.05, 1.03]
Seto 2003	0/13	83/241		11.3 %	0.07 [0.00, 1.20]
Teleman 2004	5/36	13/50		12.0 %	0.46 [0.15, 1.43]
Yin 2004	27/77	128/180		63.9 %	0.22 [0.12, 0.39]
Total (95% CI)	**151**	**561**		**100.0 %**	**0.23 [0.14, 0.37]**

Total events: 34 (Cases), 249 (Control)

Heterogeneity: Chi^2 = 2.10, df = 3 (P = 0.55); I^2 =0.0%

Test for overall effect: Z = 5.99 (P < 0.00001)

0.1   1   10

Favours gowns   Favours control

Analysis 1.7. Comparison 1 Case control studies, Outcome 7 All interventions.

Review: Interventions for the interruption or reduction of the spread of respiratory viruses
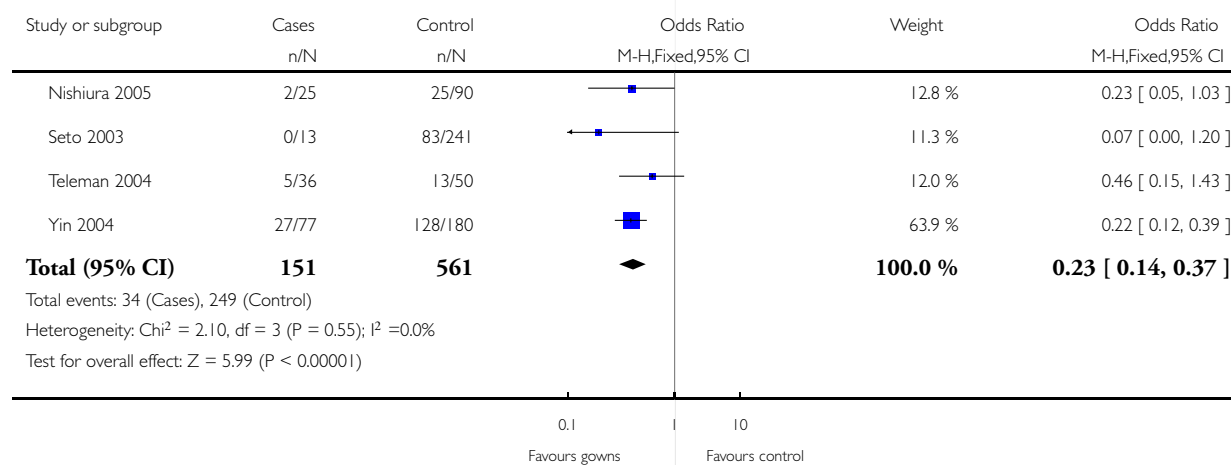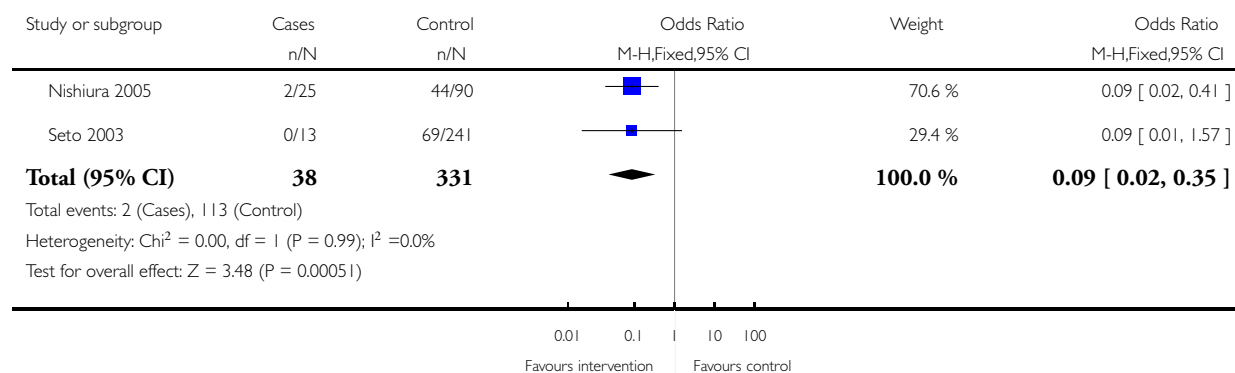
Comparison: 1 Case control studies

Outcome: 7 All interventions

Study or subgroup	Cases n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Nishiura 2005	2/25	44/90		70.6 %	0.09 [0.02, 0.41]
Seto 2003	0/13	69/241		29.4 %	0.09 [0.01, 1.57]
Total (95% CI)	**38**	**331**		**100.0 %**	**0.09 [0.02, 0.35]**

Total events: 2 (Cases), 113 (Control)

Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.99); I^2 =0.0%

Test for overall effect: Z = 3.48 (P = 0.00051)

```
        0.01      0.1     1     10    100
      Favours intervention      Favours control
```

WHAT'S NEW

Last assessed as up-to-date: 19 November 2006

Date	Event	Description
8 July 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 2006

Review first published: Issue 4, 2007

CONTRIBUTIONS OF AUTHORS

Ruth Foxlee (RF) and Alex Rivetti (AR) were responsible for constructing the search strategies.

Tom Jefferson (TOJ), Chris Del Mar (CDM) and Liz Dooley (LD) were responsible for drafting the protocol.

TOJ, Eliana Ferroni (FE), Bill Hewak (BH) and Adi Prabhala (AP) extracted study data.

Sree Nair (SN) performed the analyses.

TOJ and CDM wrote the final report. All authors contributed to the final report.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- The Cochrane Collaboration Steering Group, UK.

External sources

- NHS R&D programme, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Influenza, Human [transmission; virology]; Respiratory Tract Infections [*prevention & control; *virology]; Virus Diseases [*prevention & control; transmission]

MeSH check words

Humans