
Nonpharmaceutical Measures for Pandemic Influenza in Nonhealthcare Settings—Personal Protective and Environmental Measures

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There were 3 influenza pandemics in the 20th century, and there has been 1 so far in the 21st century. Local, national, and international health authorities regularly update their plans for mitigating the next influenza pandemic in light of the latest available evidence on the effectiveness of various control measures in reducing transmission. Here, we review the evidence base on the effectiveness of nonpharmaceutical personal protective measures and environmental hygiene measures in nonhealthcare settings and discuss their potential inclusion in pandemic plans. Although mechanistic studies support the potential effect of hand hygiene or face masks, evidence from 14 randomized controlled trials of these measures did not support a substantial effect on transmission of laboratory-confirmed influenza. We similarly found limited evidence on the effectiveness of improved hygiene and environmental cleaning. We identified several major knowledge gaps requiring further research, most fundamentally an improved characterization of the modes of person-to-person transmission.

Influenza pandemics occur at irregular intervals when new strains of influenza A virus spread in humans (1). Influenza pandemics cause considerable health and social impact that exceeds that of typical seasonal (interpandemic) influenza epidemics. One of the characteristics of influenza pandemics is the high incidence of infections in all age groups because of the lack of population immunity. Although influenza vaccines are the cornerstone of seasonal influenza control, specific vaccines for a novel pandemic strain are not expected to be available for the first 5–6 months of the next pandemic. Antiviral drugs will be available in some locations to treat more severe infections but are unlikely to be available in the

quantities that might be required to control transmission in the general community. Thus, efforts to control the next pandemic will rely largely on nonpharmaceutical interventions.

Most influenza virus infections cause mild and self-limiting disease; only a small fraction of case-patients require hospitalization. Therefore, influenza virus infections spread mainly in the community. Influenza virus is believed to be transmitted predominantly by respiratory droplets, but the size distribution of particles responsible for transmission remains unclear, and in particular, there is a lack of consensus on the role of fine particle aerosols in transmission (2,3). In healthcare settings, droplet precautions are recommended in addition to standard precautions for healthcare personnel when interacting with influenza patients and for all visitors during influenza seasons (4). Outside healthcare settings, hand hygiene is recommended in most national pandemic plans (5), and medical face masks were a common sight during the influenza pandemic in 2009. Hand hygiene has been proven to prevent many infectious diseases and might be considered a major component in influenza pandemic plans, whether or not it has proven effectiveness against influenza virus transmission, specifically because of its potential to reduce other infections and thereby reduce pressure on healthcare services.

In this article, we review the evidence base for personal protective measures and environmental hygiene measures, and specifically the evidence for the effectiveness of these measures in reducing transmission of laboratory-confirmed influenza in the community. We also discuss the implications of the evidence base for inclusion of these measures in pandemic plans.

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Methods and Results

We conducted systematic reviews to evaluate the effectiveness of personal protective measures on influenza virus transmission, including hand hygiene, respiratory etiquette, and face masks, and a systematic review of surface and object cleaning as an environmental measure (Table 1). We searched 4 databases (Medline, PubMed, EMBASE, and CENTRAL) for literature in all languages. We aimed to identify randomized controlled trials (RCTs) of each measure for laboratory-confirmed influenza outcomes for each of the measures because RCTs provide the highest quality of evidence. For respiratory etiquette and surface and object cleaning, because of a lack of RCTs for laboratory-confirmed influenza, we also searched for RCTs reporting effects of these interventions on influenza-like illness (ILI) and respiratory illness outcomes and then for observational studies on laboratory-confirmed influenza, ILI, and respiratory illness outcomes. For each review, 2 authors (E.Y.C.S. and J.X.) screened titles and abstracts and reviewed full texts independently.

We performed meta-analysis for hand hygiene and face mask interventions and estimated the effect of these measures on laboratory-confirmed influenza prevention by risk ratios (RRs). We used a fixed-effects model to estimate the overall effect in a pooled analysis or subgroup analysis. No overall effect would be generated if there was considerable heterogeneity on the basis of I^2 statistic $\geq 75\%$ (6). We performed quality assessment of evidence on hand hygiene and face mask interventions by using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (7). We provide additional details of the search strategies, selection of articles, summaries of the selected articles, and

quality assessment (Appendix, <https://wwwnc.cdc.gov/EID/article/26/5/19-0994-App1.pdf>).

Personal Protective Measures

Hand Hygiene

We identified a recent systematic review by Wong et al. on RCTs designed to assess the efficacy of hand hygiene interventions against transmission of laboratory-confirmed influenza (8). We used this review as a starting point and then searched for additional literature published after 2013; we found 3 additional eligible articles published during the search period of January 1, 2013–August 13, 2018. In total, we identified 12 articles (9–20), of which 3 articles were from the updated search and 9 articles from Wong et al. (8). Two articles relied on the same underlying dataset (16,19); therefore, we counted these 2 articles as 1 study, which resulted in 11 RCTs. We further selected 10 studies with >10,000 participants for inclusion in the meta-analysis (Figure 1). We excluded 1 study from the meta-analysis because it provided estimates of infection risks only at the household level, not the individual level (20). We did not generate an overall pooled effect of hand hygiene only or of hand hygiene with or without face mask because of high heterogeneity in individual estimates (I^2 87 and 82%, respectively). The effect of hand hygiene combined with face masks on laboratory-confirmed influenza was not statistically significant (RR 0.91, 95% CI 0.73–1.13; $I^2 = 35\%$, $p = 0.39$). Some studies reported being underpowered because of limited sample size, and low adherence to hand hygiene interventions was observed in some studies.

We further analyzed the effect of hand hygiene by setting because transmission routes might vary

Table 1. Summary of literature searches for systematic review on personal and environmental nonpharmaceutical interventions for pandemic influenza*

Types of interventions	No. studies identified	Study designs included†	Main findings
Hand hygiene	12	RCT	The evidence from RCTs suggested that hand hygiene interventions do not have a substantial effect on influenza transmission.
Respiratory etiquette	0	NA	We did not identify research evaluating the effectiveness of respiratory etiquette on influenza transmission.
Face masks	10	RCT	The evidence from RCTs suggested that the use of face masks either by infected persons or by uninfected persons does not have a substantial effect on influenza transmission.
Surface and object cleaning	3	RCT, observational studies	There was a limited amount of evidence suggesting that surface and object cleaning does not have a substantial effect on influenza transmission.

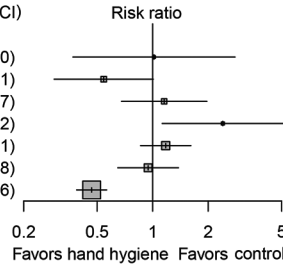
*NA, not available; RCT randomized controlled trial.

†In these systematic reviews, we prioritized RCTs, and only considered observational studies if there were a small number of RCTs. Our rationale was that with evidence from a larger number of RCTs, additional evidence from observational studies would be unlikely to change overall conclusions.

A

Author (reference)	Hand hygiene		Control		Weight	Risk ratio (95% CI)
	Events	Total	Events	Total		
Cowling et al. 2008 (12)	5	84	12	205	1.5%	1.02 (0.37–2.80)
Cowling et al. 2009 (11)	14	257	28	279	5.9%	0.54 (0.29–1.01)
Larson et al. 2010 (13)	29	946	24	904	5.4%	1.15 (0.68–1.97)
Ram et al. 2015 (14)	17	177	10	250	1.8%	2.40 (1.13–5.12)
Simmerman et al. 2011 (15)	66	292	58	302	12.6%	1.18 (0.86–1.61)
Stebbins et al. 2011 (16)	51	1,695	53	1,665	11.8%	0.95 (0.65–1.38)
Talaat et al. 2011 (18)	125	808	281	848	60.8%	0.47 (0.39–0.56)

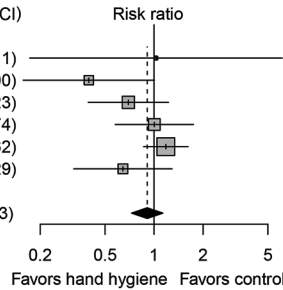
Heterogeneity: $I^2 = 87%$, $\tau^2 = 0.2837$, $p < 0.01$



B

Author (reference)	Hand hygiene		Control		Weight	Risk ratio (95% CI)
	Events	Total	Events	Total		
Aiello et al. 2010 (9)	2	316	3	487	1.6%	1.03 (0.17–6.11)
Aiello et al. 2012 (10)	6	349	16	370	10.8%	0.40 (0.16–1.00)
Cowling et al. 2009 (11)	18	258	28	279	18.8%	0.70 (0.39–1.23)
Larson et al. 2010 (13)	25	938	24	904	17.1%	1.00 (0.58–1.74)
Simmerman et al. 2011 (15)	66	291	58	302	39.7%	1.18 (0.86–1.62)
Suess et al. 2012 (17)	10	67	19	82	11.9%	0.64 (0.32–1.29)

Fixed effect model
 Heterogeneity: $I^2 = 35%$, $\tau^2 = 0.0511$, $p = 0.17$
 Test for overall effect: $z = -0.85$ ($p = 0.39$)



C

Author (reference)	Hand hygiene		Control		Weight	Risk ratio (95% CI)
	Events	Total	Events	Total		
Aiello et al. 2010 (9)	2	316	3	487	0.5%	1.03 (0.17–6.11)
Aiello et al. 2012 (10)	6	349	16	370	3.0%	0.40 (0.16–1.00)
Cowling et al. 2008 (12)	5	84	12	205	1.3%	1.02 (0.37–2.80)
Cowling et al. 2009 (11)	32	515	28	279	6.9%	0.62 (0.38–1.01)
Larson et al. 2010 (13)	54	1,884	24	904	6.2%	1.08 (0.67–1.73)
Ram et al. 2015 (14)	17	177	10	250	1.6%	2.40 (1.13–5.12)
Simmerman et al. 2011 (15)	132	583	58	302	14.6%	1.18 (0.89–1.55)
Stebbins et al. 2011 (16)	51	1,695	53	1,665	10.2%	0.95 (0.65–1.38)
Suess et al. 2012 (17)	10	67	19	82	3.3%	0.64 (0.32–1.29)
Talaat et al. 2011 (18)	125	808	281	848	52.4%	0.47 (0.39–0.56)

Heterogeneity: $I^2 = 82%$, $\tau^2 = 0.2286$, $p < 0.01$

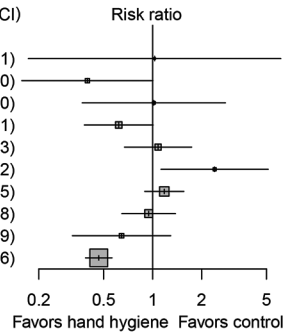


Figure 1. Meta-analysis of risk ratios for the effect of hand hygiene with or without face mask use on laboratory-confirmed influenza from 10 randomized controlled trials with >11,000 participants. A) Hand hygiene alone; B) hand hygiene and face mask; C) hand hygiene with or without face mask. Pooled estimates were not made if there was high heterogeneity ($I^2 \geq 75%$). Squares indicate risk ratio for each of the included studies, horizontal line indicates 95% CIs, dashed vertical line indicates pooled estimation of risk ratio, and diamond indicates pooled estimation of risk ratio. Diamond width corresponds to the 95% CI.

in different settings. We found 6 studies in household settings examining the effect of hand hygiene with or without face masks, but the overall pooled effect was not statistically significant (RR 1.05, 95% CI 0.86–1.27; $I^2 = 57%$, $p = 0.65$) (Appendix Figure 4) (11–15,17). The findings of 2 studies in school settings were different (Appendix Figure 5). A study conducted in the United States (16) showed no major effect of hand hygiene, whereas a study in Egypt (18) reported that hand hygiene reduced the risk for influenza by >50%. A pooled analysis of 2 studies in university residential halls reported a marginally significant protective effect of a combination of hand hygiene plus face masks worn by all residents (RR 0.48, 95% CI 0.21–1.08; $I^2 = 0%$, $p = 0.08$) (Appendix Figure 6) (9,10).

In support of hand hygiene as an effective measure, experimental studies have reported that

influenza virus could survive on human hands for a short time and could transmit between hands and contaminated surfaces (2,21). Some field studies reported that influenza A(H1N1)pdm09 and influenza A(H3N2) virus RNA and viable influenza virus could be detected on the hands of persons with laboratory-confirmed influenza (22,23), supporting the potential of direct and indirect contact transmission to play a role in the spread of influenza. Other experimental studies also demonstrated that hand hygiene could reduce or remove infectious influenza virus from human hands (24,25). However, results from our meta-analysis on RCTs did not provide evidence to support a protective effect of hand hygiene against transmission of laboratory-confirmed influenza. One study did report a major effect, but in this trial of hand hygiene in schools in Egypt, running water had to be installed and soap and hand-drying

material had to be introduced into the intervention schools as part of the project (18). Therefore, the impact of hand hygiene might also be a reflection of the introduction of soap and running water into primary schools in a lower-income setting. If one considers all of the evidence from RCTs together, it is useful to note that some studies might have underestimated the true effect of hand hygiene because of the complexity of implementing these intervention studies. For instance, the control group would not typically have zero knowledge or use of hand hygiene, and the intervention group might not adhere to optimal hand hygiene practices (11,13,15).

Hand hygiene is also effective in preventing other infectious diseases, including diarrheal diseases and some respiratory diseases (8,26). The need for hand hygiene in disease prevention is well recognized among most communities. Hand hygiene has been accepted as a personal protective measure in >50% of national preparedness plans for pandemic influenza (5). Hand hygiene practice is commonly performed with soap and water, alcohol-based hand rub, or other waterless hand disinfectants, all of which are easily accessible, available, affordable, and well accepted in most communities. However, resource limitations in some areas are a concern when clean running water or alcohol-based hand rub are not available. There are few adverse effects of hand hygiene except for skin irritation caused by some hand hygiene products (27). However, because of certain social or religious practices, alcohol-based hand sanitizers might not be permitted in some locations (28). Compliance with proper hand hygiene practice tends to be low because habitual behaviors are difficult to change (29). Therefore, hand hygiene promotion programs are needed to advocate and encourage proper and effective hand hygiene.

Respiratory Etiquette

Respiratory etiquette is defined as covering the nose and mouth with a tissue or a mask (but not a hand) when coughing or sneezing, followed by proper disposal of used tissues, and proper hand hygiene after contact with respiratory secretions (30). Other descriptions of this measure have included turning the head and covering the mouth when coughing and coughing or sneezing into a sleeve or elbow, rather than a hand. The rationale for not coughing into hands is to prevent subsequent contamination of other surfaces or objects (31). We conducted a search on November 6, 2018, and identified literature that was available in the databases during 1946–November 5, 2018. We did not identify any published research on

the effectiveness of respiratory etiquette in reducing the risk for laboratory-confirmed influenza or ILI. One observational study reported a similar incidence rate of self-reported respiratory illness (defined by >1 symptoms: cough, congestion, sore throat, sneezing, or breathing problems) among US pilgrims with or without practicing respiratory etiquette during the Hajj (32). The authors did not specify the type of respiratory etiquette used by participants in the study. A laboratory-based study reported that common respiratory etiquette, including covering the mouth by hands, tissue, or sleeve/arm, was fairly ineffective in blocking the release and dispersion of droplets into the surrounding environment on the basis of measurement of emitted droplets with a laser diffraction system (31).

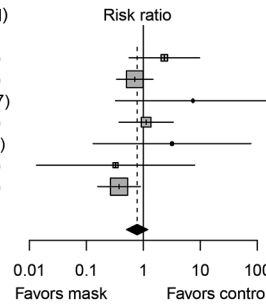
Respiratory etiquette is often listed as a preventive measure for respiratory infections. However, there is a lack of scientific evidence to support this measure. Whether respiratory etiquette is an effective nonpharmaceutical intervention in preventing influenza virus transmission remains questionable, and worthy of further research.

Face Masks

In our systematic review, we identified 10 RCTs that reported estimates of the effectiveness of face masks in reducing laboratory-confirmed influenza virus infections in the community from literature published during 1946–July 27, 2018. In pooled analysis, we found no significant reduction in influenza transmission with the use of face masks (RR 0.78, 95% CI 0.51–1.20; $I^2 = 30%$, $p = 0.25$) (Figure 2). One study evaluated the use of masks among pilgrims from Australia during the Hajj pilgrimage and reported no major difference in the risk for laboratory-confirmed influenza virus infection in the control or mask group (33). Two studies in university settings assessed the effectiveness of face masks for primary protection by monitoring the incidence of laboratory-confirmed influenza among student hall residents for 5 months (9,10). The overall reduction in ILI or laboratory-confirmed influenza cases in the face mask group was not significant in either studies (9,10). Study designs in the 7 household studies were slightly different: 1 study provided face masks and P2 respirators for household contacts only (34), another study evaluated face mask use as a source control for infected persons only (35), and the remaining studies provided masks for the infected persons as well as their close contacts (11–13,15,17). None of the household studies reported a significant reduction in secondary laboratory-confirmed influenza virus infections in the face

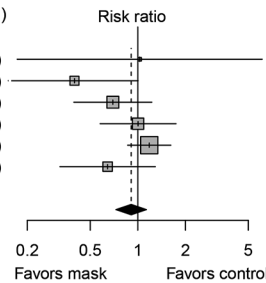
A

Author (reference)	Mask		Control		Weight	Risk ratio (95% CI)
	Events	Total	Events	Total		
Aiello et al. 2010 (19)	5	347	3	487	5.7%	2.34 (0.56–9.72)
Aiello et al. 2012 (10)	12	392	16	370	37.3%	0.71 (0.34–1.48)
Barasheed et al. 2014 (33)	1	11	0	28	0.7%	7.43 (0.33–169.47)
Cowling et al. 2008 (12)	4	61	12	205	12.5%	1.12 (0.37–3.35)
MacIntyre et al. 2009 (34)	1	94	0	100	1.1%	3.19 (0.13–77.36)
MacIntyre et al. 2016 (35)	0	302	1	295	3.4%	0.33 (0.01–7.96)
Suess et al. 2012 (17)	6	69	19	82	39.4%	0.38 (0.16–0.89)
Fixed effect model	1,276		1,567		100.0%	0.78 (0.51–1.20)
Heterogeneity: $I^2 = 30\%$, $\tau^2 = 0.1899$, $p = 0.20$						
Test for overall effect: $z = -1.15$ ($p = 0.25$)						



B

Author (reference)	Mask		Control		Weight	Risk ratio (95% CI)
	Events	Total	Events	Total		
Aiello et al. 2010 (9)	2	316	3	487	1.6%	1.03 (0.17–6.11)
Aiello et al. 2012 (10)	6	349	16	370	10.8%	0.40 (0.16–1.00)
Cowling et al. 2009 (11)	18	258	28	279	18.8%	0.70 (0.39–1.23)
Larson et al. 2010 (13)	25	938	24	904	17.1%	1.00 (0.58–1.74)
Simmerman et al. 2011 (15)	66	291	58	302	39.7%	1.18 (0.86–1.62)
Suess et al. 2012 (17)	10	67	19	82	11.9%	0.64 (0.32–1.29)
Fixed effect model	2,219		2,424		100.0%	0.91 (0.73–1.13)
Heterogeneity: $I^2 = 35\%$, $\tau^2 = 0.0511$, $p = 0.17$						
Test for overall effect: $z = -0.85$ ($p = 0.39$)						



C

Author (reference)	Mask		Control		Weight	Risk ratio (95% CI)
	Events	Total	Events	Total		
Aiello et al. 2010 (9)	7	663	3	487	2.1%	1.71 (0.45–6.59)
Aiello et al. 2012 (10)	18	741	16	370	13.0%	0.56 (0.29–1.09)
Barasheed et al. 2014 (33)	1	11	0	28	0.2%	7.43 (0.33–169.47)
Cowling et al. 2009 (11)	18	258	28	279	16.3%	0.70 (0.39–1.23)
Cowling et al. 2008 (12)	4	61	12	205	3.3%	1.12 (0.37–3.35)
Larson et al. 2010 (13)	25	938	24	904	14.9%	1.00 (0.58–1.74)
MacIntyre et al. 2009 (34)	1	94	0	100	0.3%	3.19 (0.13–77.36)
MacIntyre et al. 2016 (35)	0	302	1	295	0.9%	0.33 (0.01–7.96)
Simmerman et al. 2011 (15)	66	291	58	302	34.6%	1.18 (0.86–1.62)
Suess et al. 2012 (17)	16	136	19	82	14.4%	0.51 (0.28–0.93)
Fixed effect model	3,495		3,052		100.0%	0.92 (0.75–1.12)
Heterogeneity: $I^2 = 30\%$, $\tau^2 = 0.0593$, $p = 0.17$						
Test for overall effect: $z = -0.84$ ($p = 0.40$)						

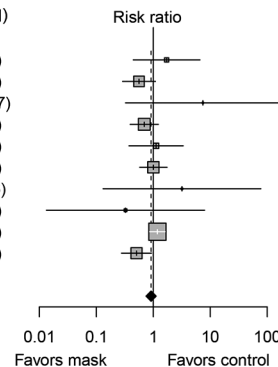


Figure 2. Meta-analysis of risk ratios for the effect of face mask use with or without enhanced hand hygiene on laboratory-confirmed influenza from 10 randomized controlled trials with >6,500 participants. A) Face mask use alone; B) face mask and hand hygiene; C) face mask with or without hand hygiene. Pooled estimates were not made if there was high heterogeneity ($I^2 \geq 75\%$). Squares indicate risk ratio for each of the included studies, horizontal lines indicate 95% CIs, dashed vertical lines indicate pooled estimation of risk ratio, and diamonds indicate pooled estimation of risk ratio. Diamond width corresponds to the 95% CI.

mask group (11–13,15,17,34,35). Most studies were underpowered because of limited sample size, and some studies also reported suboptimal adherence in the face mask group.

Disposable medical masks (also known as surgical masks) are loose-fitting devices that were designed to be worn by medical personnel to protect accidental contamination of patient wounds, and to protect the wearer against splashes or sprays of bodily fluids (36). There is limited evidence for their effectiveness in preventing influenza virus transmission either when worn by the infected person for source control or when worn by uninfected persons to reduce exposure. Our systematic review found no significant effect of face masks on transmission of laboratory-confirmed influenza.

We did not consider the use of respirators in the community. Respirators are tight-fitting masks that can protect the wearer from fine particles (37) and should provide better protection against influenza virus exposures when properly worn because of higher filtration efficiency. However, respirators, such as N95 and P2 masks, work best when they are fit-tested, and these masks will be in limited supply during the next pandemic. These specialist devices should be reserved for use in healthcare settings or in special subpopulations such as immunocompromised persons in the community, first responders, and those performing other critical community functions, as supplies permit.

In lower-income settings, it is more likely that reusable cloth masks will be used rather than

disposable medical masks because of cost and availability (38). There are still few uncertainties in the practice of face mask use, such as who should wear the mask and how long it should be used for. In theory, transmission should be reduced the most if both infected members and other contacts wear masks, but compliance in uninfected close contacts could be a problem (12,34). Proper use of face masks is essential because improper use might increase the risk for transmission (39). Thus, education on the proper use and disposal of used face masks, including hand hygiene, is also needed.

Environmental Measures

Surface and Object Cleaning

For the search period from 1946 through October 14, 2018, we identified 2 RCTs and 1 observational study about surface and object cleaning measures for inclusion in our systematic review (40–42). One RCT conducted in day care nurseries found that bi-weekly cleaning and disinfection of toys and linen reduced the detection of multiple viruses, including adenovirus, rhinovirus, and respiratory syncytial virus in the environment, but this intervention was not significant in reducing detection of influenza virus, and it had no major protective effect on acute respiratory illness (41). Another RCT found that hand hygiene with hand sanitizer together with surface disinfection reduced absenteeism related to gastrointestinal illness in elementary schools, but there was no major reduction in absenteeism related to respiratory illness (42). A cross-sectional study found that passive contact with bleach was associated with a major increase in self-reported influenza (40).

Given that influenza virus can survive on some surfaces for prolonged periods (43), and that cleaning or disinfection procedures can effectively reduce or inactivate influenza virus from surfaces and objects in experimental studies (44), there is a theoretical basis to believe that environmental cleaning could reduce influenza transmission. As an illustration of this proposal, a modeling study estimated that cleaning of extensively touched surfaces could reduce influenza A infection by 2% (45). However, most studies of influenza virus in the environment are based on detection of virus RNA by PCR, and few studies reported detection of viable virus.

Although we found no evidence that surface and object cleaning could reduce influenza transmission, this measure does have an established impact on prevention of other infectious diseases (42).

It should be feasible to implement this measure in most settings, subject to the availability of water and cleaning products. Although irritation caused by cleaning products is limited, safety remains a concern because some cleaning products can be toxic or cause allergies (40).

Discussion

In this review, we did not find evidence to support a protective effect of personal protective measures or environmental measures in reducing influenza transmission. Although these measures have mechanistic support based on our knowledge of how influenza is transmitted from person to person, randomized trials of hand hygiene and face masks have not demonstrated protection against laboratory-confirmed influenza, with 1 exception (18). We identified only 2 RCTs on environmental cleaning and no RCTs on cough etiquette.

Hand hygiene is a widely used intervention and has been shown to effectively reduce the transmission of gastrointestinal infections and respiratory infections (26). However, in our systematic review, updating the findings of Wong et al. (8), we did not find evidence of a major effect of hand hygiene on laboratory-confirmed influenza virus transmission (Figure 1). Nevertheless, hand hygiene might be included in influenza pandemic plans as part of general hygiene and infection prevention.

We did not find evidence that surgical-type face masks are effective in reducing laboratory-confirmed influenza transmission, either when worn by infected persons (source control) or by persons in the general community to reduce their susceptibility (Figure 2). However, as with hand hygiene, face masks might be able to reduce the transmission of other infections and therefore have value in an influenza pandemic when healthcare resources are stretched.

It is essential to note that the mechanisms of person-to-person transmission in the community have not been fully determined. Controversy remains over the role of transmission through fine-particle aerosols (3,46). Transmission by indirect contact requires transfer of viable virus from respiratory mucosa onto hands and other surfaces, survival on those surfaces, and successful inoculation into the respiratory mucosa of another person. All of these components of the transmission route have not been studied extensively. The impact of environmental factors, such as temperature and humidity, on influenza transmission is also uncertain (47). These uncertainties over basic transmission modes and mechanisms hinder the optimization of control measures.

Table 2. Knowledge gaps for personal protective and environmental nonpharmaceutical interventions for pandemic influenza*

Intervention	Knowledge gaps	Suggested studies
Hand hygiene	There are major gaps in our knowledge of the mechanisms of person-to-person transmission of influenza, including the role of direct and indirect contact, the degree of viral contamination on hands and various types of surfaces in different settings, and the potential for contact transmission to occur in different locations and under different environmental conditions. There is little information on whether greater reductions in transmission could be possible with combinations of personal intervention (e.g., isolation away from family members as much as possible, plus using face masks and enhancing hand hygiene).	Additional high-quality RCTs of efficacy of hand hygiene against laboratory-confirmed influenza in other nonhealthcare settings, except households and university residential halls, would be valuable. In particular, studies in school settings are needed to solve the discrepancy between the two studies from the United States and Egypt.
Respiratory etiquette	There is no evidence about the quantitative effectiveness of respiratory etiquette against influenza virus.	RCTs of interventions to demonstrate the effectiveness of respiratory etiquette in reducing influenza transmission would be valuable.
Face mask	There are major gaps in our knowledge of the mechanisms of person-to-person transmission of influenza, including the importance of transmission through droplets of different sizes including small particle aerosols, and the potential for droplet and aerosol transmission to occur in different locations and with environmental conditions.	Additional high-quality RCTs of efficacy of face masks against laboratory-confirmed influenza would be valuable. Effectiveness of face masks or respirator use to prevent influenza prevention in special subpopulation, such as immunocompromised persons, would be valuable.
Surface and object cleaning	The effectiveness of different cleaning products in preventing influenza transmission—in terms of cleaning frequency, cleaning dosage, cleaning time point, and cleaning targeted surface and object material—remains unknown.	RCTs of interventions to demonstrate the effectiveness of surface and object cleaning in reducing influenza transmission would be valuable. Studies that can demonstrate the reduction of environmental detection of influenza virus through cleaning of surfaces and objects would also be valuable.

*RCT, randomized control trial.

In this review, we focused on 3 personal protective measures and 1 environmental measure. Other potential environmental measures include humidification in dry environments (48), increasing ventilation (49), and use of upper-room UV light (50), but there is limited evidence to support these measures. Further investigations on the effectiveness of respiratory etiquette and surface cleaning through conducting RCTs would be helpful to provide evidence with higher quality; evaluation of the effectiveness of these measures targeting specific population groups, such as immunocompromised persons, would also be beneficial (Table 2). Future cost-effectiveness evaluations could provide more support for the potential use of these measures. Further research on transmission modes and alternative interventions to reduce influenza transmission would be valuable in improving pandemic preparedness. Finally, although our review focused on nonpharmaceutical measures to be taken during influenza pandemics, the findings could also apply to severe seasonal influenza epidemics. Evidence from RCTs of hand hygiene or face masks did not support a substantial effect on transmission of laboratory-confirmed influenza, and limited evidence was available on other environmental measures.

This study was conducted in preparation for the development of guidelines by the World Health Organization on the use of nonpharmaceutical interventions for pandemic influenza in nonmedical settings.

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Nonpharmaceutical Measures for Pandemic Influenza in Nonhealthcare Settings— Personal Protective and Environmental Measures

Appendix

Hand Hygiene

Terminology

Relevant terminology relating to hand hygiene are shown as follows (Appendix Table 1):

Appendix Table 1. Definition of terms relevant to hand hygiene

Term	Definition
Hand hygiene practices	
Hand hygiene	“A general term referring to any action of hand cleansing” (e.g., handwashing, antiseptic handwash, antiseptic hand rub and surgical hand antisepsis) (1,2)
Hand cleansing	“Action of performing hand hygiene for the purpose of physically or mechanically removing dirt, organic material, and/or microorganisms” (1)
Handwashing	“Washing hands with plain or antimicrobial soap and water” (1)
Antiseptic handwashing	“Washing hands with soap and water, or other detergents containing an antiseptic agent” (1)
Antiseptic handrubbing (or handrubbing)	Applying an antiseptic handrub to all surfaces of the hands “to reduce or inhibit the growth of microorganisms without the need for an exogenous source of water and requiring no rinsing or drying with towels or other devices” (1,2)
Hand disinfection	“Hand disinfection is extensively used as a term in some parts of the world and can refer to antiseptic handwash, antiseptic handrubbing, hand antisepsis/decontamination/degerming, handwashing with an antimicrobial soap and water, hygienic hand antisepsis, or hygienic handrub” (1)
Hand hygiene products	
Alcohol-based (hand) rub (or hand sanitizer)	“An alcohol-containing preparation (liquid, gel or foam) designed for application to the hands to inactivate microorganisms and/or temporarily suppress their growth. Such preparations may contain one or more types of alcohol, other active ingredients with excipients, and humectants” (1)
Antimicrobial (medicated) soap	“Soap (detergent) containing an antiseptic agent at a concentration sufficient to inactivate microorganisms and/or temporarily suppress their growth. The detergent activity of such soaps may also dislodge transient microorganisms or other contaminants from the skin to facilitate their subsequent removal by water” (1)
Antiseptic hand wipe	“A piece of fabric or paper pre-wetted with an antiseptic used for wiping hands to inactivate and/or remove microbial contamination. They may be considered as an alternative to washing hands with non-antimicrobial soap and water but, because they are not as effective at reducing bacterial counts on HCWs’ hands as alcohol-based handrubs or washing hands with an antimicrobial soap and water, they are not a substitute for using an alcohol-based handrub or antimicrobial soap” (1)
Plain soap	“Plain soap refers to detergents that do not contain antimicrobial agents or contain low concentrations of antimicrobial agents that are effective solely as preservatives” (2)
Other	
Visibly soiled hands	“Hands showing visible dirt or visibly contaminated with proteinaceous material, blood, or other body fluids (e.g., fecal material or urine)” (2)

Search Strategy

We conducted a review of systematic review on 1 August 2018 using the following search terms (Appendix Table 2) to identify literatures that were available from 1946 through July 31, 2018. Four databases (PubMed, Medline, EMBASE, and CENTRAL) were searched. Review selection criteria are systematic reviews published within 5 years studying the effect of hand hygiene interventions on prevention of laboratory-confirmed influenza in community settings. We reviewed literatures of all languages.

Appendix Table 2. Search strategy for hand hygiene

Search terms	Search date	Reviewers
#1: "hand hygiene" OR "hand washing" OR "handwashing" OR "hand-washing" OR "hand-wash" OR "hand wash" OR "handwash" OR "hand sanitize" OR "hand sanitizers" OR "hand sanitizer" OR "hand rub" OR "handrub" OR "hand rubbing" OR "hand cleansing" OR "hand cleans" OR "hand cleanser" OR "hand disinfectant" OR "hand disinfectants" OR "hand disinfection" OR "hand soap" OR "hand wipe"	August 1, 2018 for review of systematic review and August 14, 2018 for additional search	J.X. E.S.
#2: "influenza" OR "flu"		
#3: #1 AND #2		

After identifying the most recent published systematic review, we conducted an additional literature search to capture articles of all languages that were not included in the review. The search was conducted on 14 August 2018 using the same search terms in 4 databases to identify literatures that were available during January 1, 2013–August 13, 2018. Study selection criteria are randomized control trials (RCTs) comparing the effect of hand hygiene interventions with that of no intervention in preventing laboratory-confirmed influenza infections in community settings. Study participants or clusters of participants were assigned prospectively into intervention and control groups using random allocation. A community setting was defined as an open setting without confinement or special care for patients. Articles describing any hand hygiene related interventions were included. Two reviewers (J.X. and E.S.) reviewed retrieved titles and subsequent relevant abstracts independently. Titles and abstract selected by any of the reviewers were included for subsequent screening. Both reviewers reviewed full-text and extracted data for selected studies independently. If a consensus was not reached, further discussion was held or opinion was obtained from a third reviewer.

With a substantial number of randomized controlled trials conducted on hand hygiene, we did not extend the search to observational studies, but we did note the findings from earlier systematic reviews of observational studies of hand hygiene (4–6).

Risk ratios (RRs) and their 95% confidence intervals (95% CIs) were calculated to estimate the effect of hand hygiene intervention on prevention of laboratory-confirmed influenza.

Heterogeneity of each pooled and subgroup analysis was assessed by I^2 statistics. The overall effect of each pooled and subgroup analysis was estimated by fixed-effect model. If the heterogeneity was high ($I^2 \geq 75\%$), we did not estimate an overall pooled effect.

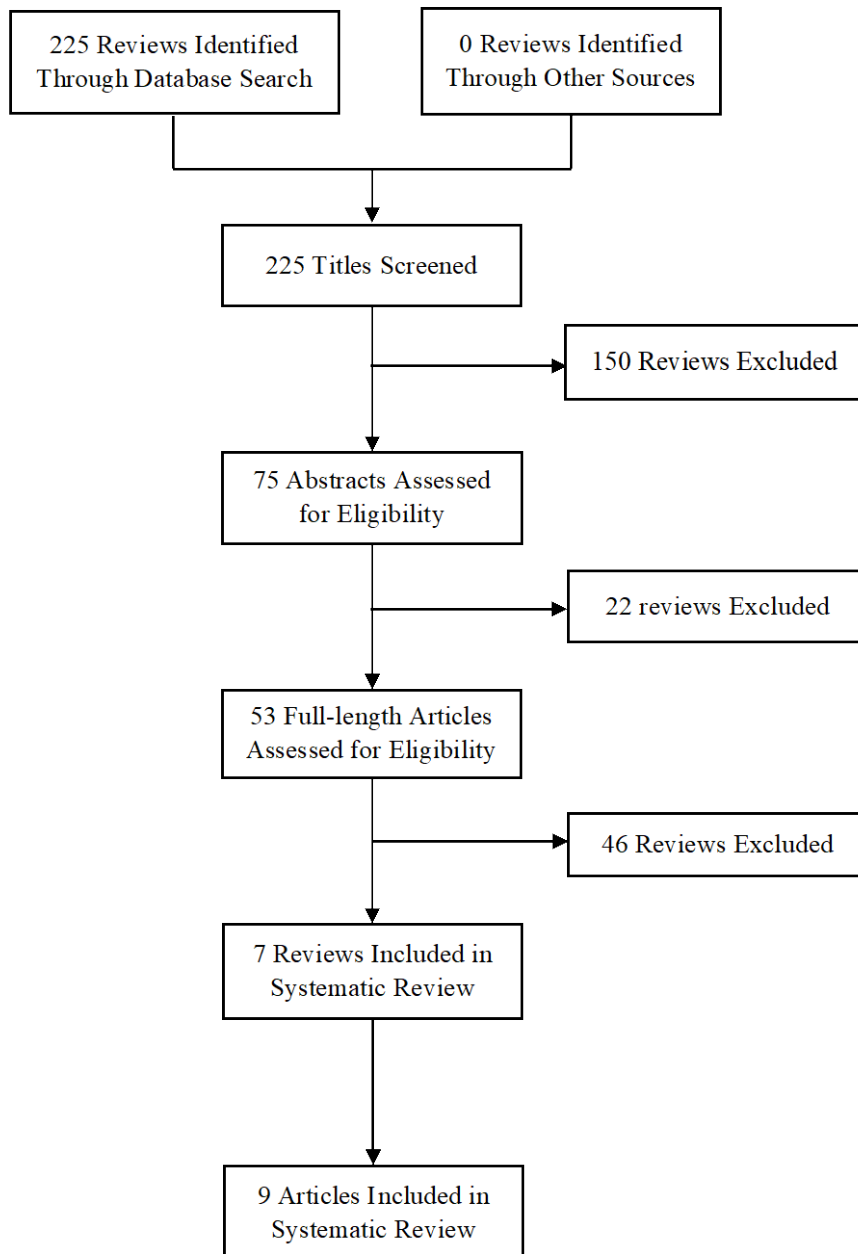
Findings

Appendix Table 3. Basic characteristics of included studies

Characteristic	No. of studies (%)
Country	
Industrialized	7 (64)
Developing	4 (36)
Setting	
Household	7 (64)
Elementary school	2 (18)
University residential hall	2 (18)
Transmission mode	
Primary	5 (45)
Secondary	6 (55)
Intervention evaluated*	
Hand sanitizer and education	3 (20)
Hand sanitizer, soap and education	1 (7)
Hand sanitizer and face mask	3 (20)
Hand sanitizer, face mask and education	2 (13)
Soap	3 (20)
Soap and education	1 (7)
Soap and face mask	2 (13)
Outcome assessed	
Laboratory-confirmed influenza	11 (100)

*More than one intervention for some studies.

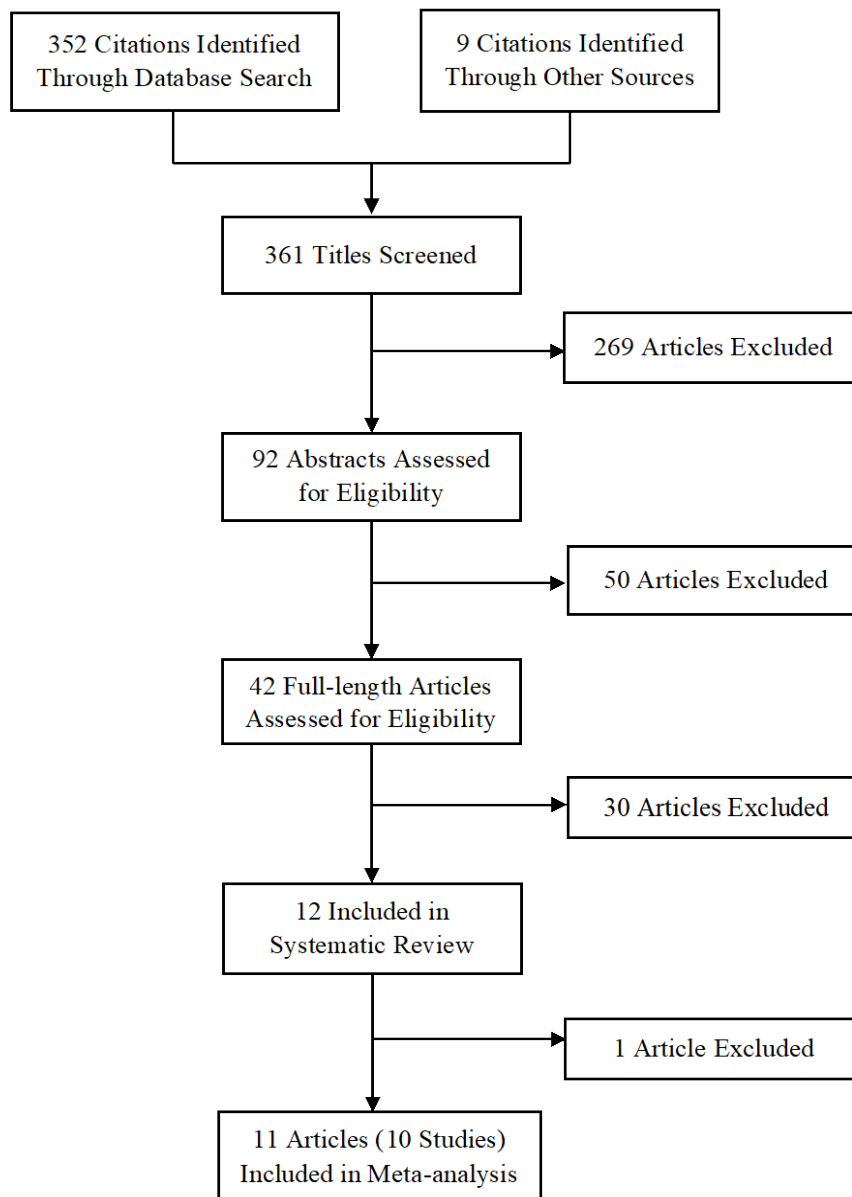
We identified 225 reviews through the search, of which 172 reviews were removed during title and abstract screening. We selected 7 reviews for our analysis after screening the full text. Reasons for exclusion included: reviews considered not systematic, reviews published outside the 5-year time frame, articles in reviews were not RCTs, and the reviews did not evaluate hand hygiene as a study intervention or laboratory-confirmed influenza infection as a study outcome. Among the 7 included reviews, we identified 9 relevant RCT studies, of which all 9 studies were included in a most recently published systematic review and metaanalysis conducted by Wong et al. (7). Therefore, we used this review as the reference base of our review of systematic review to evaluate the effect of hand hygiene in reducing the risk for laboratory-confirmed influenza virus infection. The flowchart is shown in Appendix Figure 1.



Appendix Figure 1. Flowchart of literature search and article selection for systematic reviews of the effectiveness of hand hygiene against laboratory-confirmed influenza.

Furthermore, we conducted an update search to capture literatures that were not included in the review by Wong et al. (7). We identified 352 articles from January 1, 2013 to August 13, 2018. We subsequently removed 319 articles during the title and abstract screening. Reasons for exclusion included: studies were not conducted in community settings, study design was not RCT and studies did not evaluate hand hygiene as a study intervention or laboratory-confirmed influenza infection as a study outcome. We identified 3 articles in this updated search, hence we included a total of 12 articles in our systematic review. Since two articles used the same dataset

to evaluate different research questions (8,9), we considered these articles as 1 study in our review. Moreover, one article only included secondary infection data in household level but not individual level (9), therefore we did not include this in the metaanalysis. To sum up, we included 12 articles in our systematic review and 11 articles in the metaanalysis. The flowchart is shown in Appendix Figure 2.



Appendix Figure 2. Flowchart of literature search and study selection for trials of the effectiveness of hand hygiene against laboratory-confirmed influenza.

Among the 11 studies included in the metaanalysis, 7 studies were in household settings (10–16), 2 studies in elementary school setting (9,17), and 2 studies in university residential hall

setting (18,19). Basic characteristics of the included studies are shown in Appendix Table 3, and detailed study description are shown in Appendix Table 4.

In the pooled analysis, hand hygiene with face mask (risk ratio [RR] 0.91, 95% CI 0.73–1.13; $p = 0.39$, $I^2 = 35\%$) did not have a significant protective effect in community settings (Appendix Figure 3) (11,13,15,16,18,19). Some published studies noted that poor adherence to hand hygiene might lead to underestimation of the true effect of the intervention (11,13,15).

Because the relative importance of transmission modes of influenza might vary in different settings, we conducted subgroup analysis based on various settings. In household setting (11–16), the efficacy of hand hygiene with or without face mask was not significant (RR 1.05, 95% CI 0.86–1.27; $p = 0.65$, $I^2 = 57\%$) (Appendix Figure 4). Although the pooled analysis did not identify an overall significant effect of hand hygiene, some household transmission studies reported that early implementation of hand hygiene in the index case after symptom onset might be more effective in preventing secondary infection in the household (11,16).

In school settings (9,17), total effect was not generated because of high heterogeneity (Appendix Figure 5). In a study in the United States (9), the effect of hand hygiene was not significant based on the point estimate of the RR close to 1, whereas a large trial in Egypt reported a reduction of >50% of influenza cases in the intervention group (17).

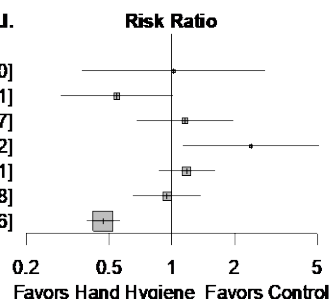
In university residential hall settings (18,19), hand hygiene with face mask intervention contributed to 52% RR reduction (RR = 0.48, 95% CI 0.21–1.08; $p = 0.08$, marginally significant, $I^2 = 0\%$) of laboratory-confirmed influenza infection (Appendix Figure 6).

The results of quality assessment of evidence on hand hygiene intervention using GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach are shown in Appendix Table 5.

Hand hygiene only

Author	Hand hygiene		Control		Weight	Risk Ratio	95% C.I.
	Events	Total	Events	Total			
Cowling et al. 2008	5	84	12	205	1.5%	1.02	[0.37; 2.80]
Cowling et al. 2009	14	257	28	279	5.9%	0.54	[0.29; 1.01]
Larson et al. 2010	29	946	24	904	5.4%	1.15	[0.68; 1.97]
Ram et al. 2015	17	177	10	250	1.8%	2.40	[1.13; 5.12]
Simmerman et al. 2011	66	292	58	302	12.6%	1.18	[0.86; 1.61]
Stebbins et al. 2011	51	1695	53	1665	11.8%	0.95	[0.65; 1.38]
Talaat et al. 2011	125	808	281	848	60.8%	0.47	[0.39; 0.56]

Heterogeneity: $I^2 = 87\%$, $\tau^2 = 0.2837$, $p < 0.01$



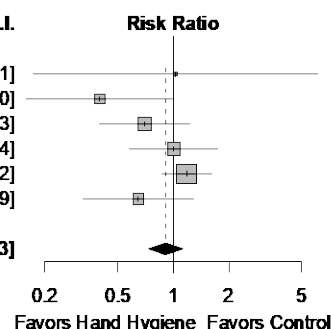
Hand hygiene and facemask

Author	Hand hygiene		Control		Weight	Risk Ratio	95% C.I.
	Events	Total	Events	Total			
Aiello et al. 2010	2	316	3	487	1.6%	1.03	[0.17; 6.11]
Aiello et al. 2012	6	349	16	370	10.8%	0.40	[0.16; 1.00]
Cowling et al. 2009	18	258	28	279	18.8%	0.70	[0.39; 1.23]
Larson et al. 2010	25	938	24	904	17.1%	1.00	[0.58; 1.74]
Simmerman et al. 2011	66	291	58	302	39.7%	1.18	[0.86; 1.62]
Suess et al. 2012	10	67	19	82	11.9%	0.64	[0.32; 1.29]

Fixed effect model **2219** **2424** **100.0%** **0.91** **[0.73; 1.13]**

Heterogeneity: $I^2 = 35\%$, $\tau^2 = 0.0511$, $p = 0.17$

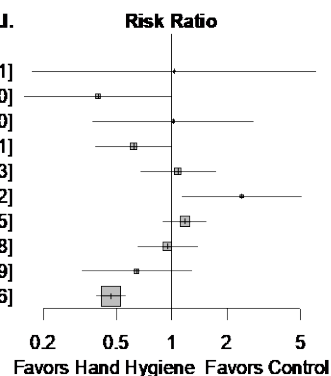
Test for overall effect: $z = -0.85$ ($p = 0.39$)



Hand hygiene with or without facemask

Author	Hand hygiene		Control		Weight	Risk Ratio	95% C.I.
	Events	Total	Events	Total			
Aiello et al. 2010	2	316	3	487	0.5%	1.03	[0.17; 6.11]
Aiello et al. 2012	6	349	16	370	3.0%	0.40	[0.16; 1.00]
Cowling et al. 2008	5	84	12	205	1.3%	1.02	[0.37; 2.80]
Cowling et al. 2009	32	515	28	279	6.9%	0.62	[0.38; 1.01]
Larson et al. 2010	54	1884	24	904	6.2%	1.08	[0.67; 1.73]
Ram et al. 2015	17	177	10	250	1.6%	2.40	[1.13; 5.12]
Simmerman et al. 2011	132	583	58	302	14.6%	1.18	[0.89; 1.55]
Stebbins et al. 2011	51	1695	53	1665	10.2%	0.95	[0.65; 1.38]
Suess et al. 2012	10	67	19	82	3.3%	0.64	[0.32; 1.29]
Talaat et al. 2011	125	808	281	848	52.4%	0.47	[0.39; 0.56]

Heterogeneity: $I^2 = 82\%$, $\tau^2 = 0.2286$, $p < 0.01$

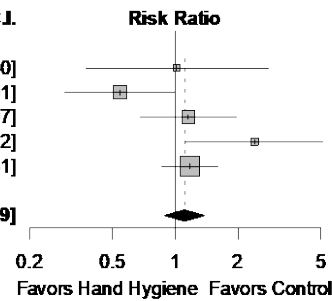


Appendix Figure 3. Metaanalysis of risk ratios for the effect of hand hygiene with or without face mask use on laboratory-confirmed influenza.

Hand hygiene only

Author	Hand hygiene		Control		Weight	Risk Ratio	95% C.I.
	Events	Total	Events	Total			
Cowling et al. 2008	5	84	12	205	5.6%	1.02	[0.37; 2.80]
Cowling et al. 2009	14	257	28	279	21.7%	0.54	[0.29; 1.01]
Larson et al. 2010	29	946	24	904	19.8%	1.15	[0.68; 1.97]
Ram et al. 2015	17	177	10	250	6.7%	2.40	[1.13; 5.12]
Simmerman et al. 2011	66	292	58	302	46.1%	1.18	[0.86; 1.61]
Fixed effect model	1756		1940		100.0%	1.11	[0.88; 1.39]

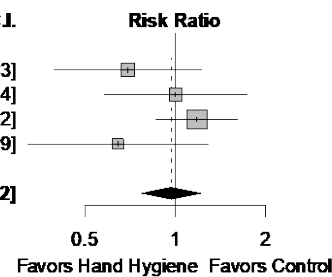
Heterogeneity: $I^2 = 57\%$, $\tau^2 = 0.1119$, $p = 0.05$
 Test for overall effect: $z = 0.89$ ($p = 0.38$)



Hand hygiene and facemask

Author	Hand hygiene		Control		Weight	Risk Ratio	95% C.I.
	Events	Total	Events	Total			
Cowling et al. 2009	18	258	28	279	21.5%	0.70	[0.39; 1.23]
Larson et al. 2010	25	938	24	904	19.5%	1.00	[0.58; 1.74]
Simmerman et al. 2011	66	291	58	302	45.4%	1.18	[0.86; 1.62]
Suess et al. 2012	10	67	19	82	13.6%	0.64	[0.32; 1.29]
Fixed effect model	1554		1567		100.0%	0.97	[0.77; 1.22]

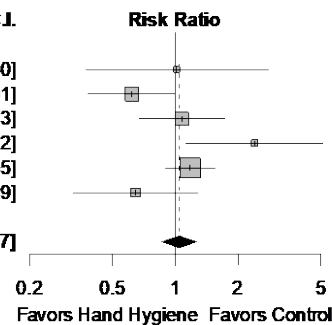
Heterogeneity: $I^2 = 28\%$, $\tau^2 = 0.0263$, $p = 0.24$
 Test for overall effect: $z = -0.27$ ($p = 0.79$)



Hand hygiene with or without facemask

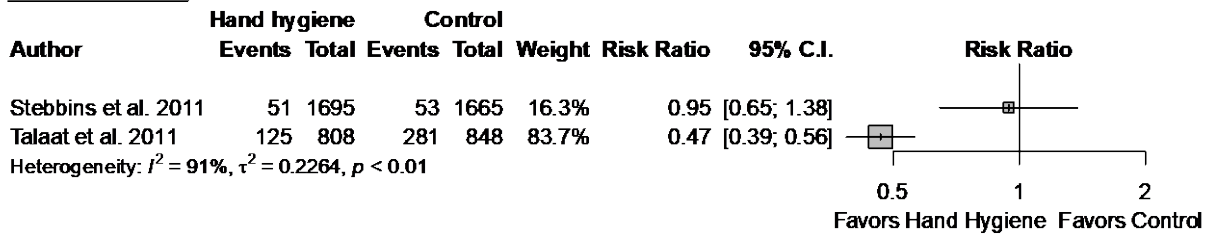
Author	Hand hygiene		Control		Weight	Risk Ratio	95% C.I.
	Events	Total	Events	Total			
Cowling et al. 2008	5	84	12	205	3.9%	1.02	[0.37; 2.80]
Cowling et al. 2009	32	515	28	279	20.5%	0.62	[0.38; 1.01]
Larson et al. 2010	54	1884	24	904	18.3%	1.08	[0.67; 1.73]
Ram et al. 2015	17	177	10	250	4.7%	2.40	[1.13; 5.12]
Simmerman et al. 2011	132	583	58	302	43.0%	1.18	[0.89; 1.55]
Suess et al. 2012	10	67	19	82	9.6%	0.64	[0.32; 1.29]
Fixed effect model	3310		2022		100.0%	1.05	[0.86; 1.27]

Heterogeneity: $I^2 = 57\%$, $\tau^2 = 0.0950$, $p = 0.04$
 Test for overall effect: $z = 0.46$ ($p = 0.65$)

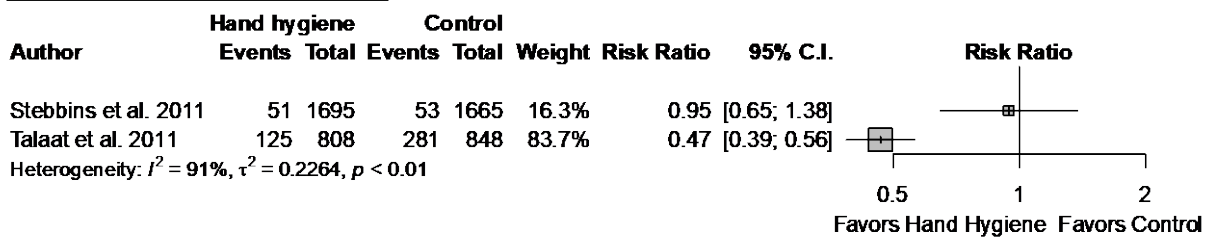


Appendix Figure 4. Metaanalysis of risk ratios for the effect of hand hygiene with or without face mask use on laboratory-confirmed influenza in household setting.

Hand hygiene only

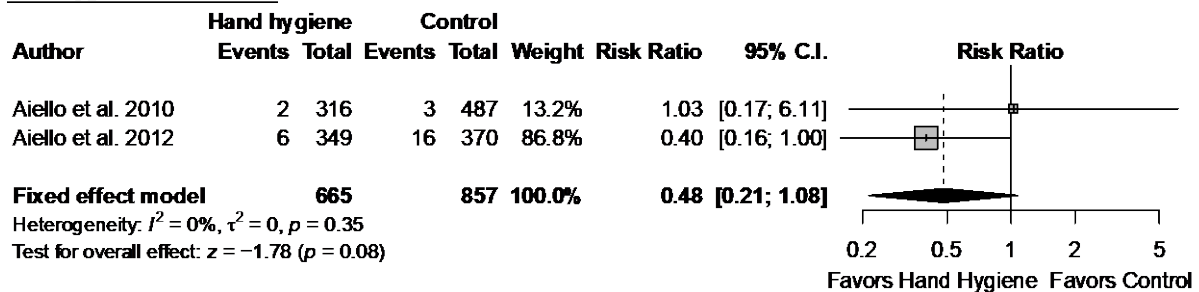


Hand hygiene with or without facemask

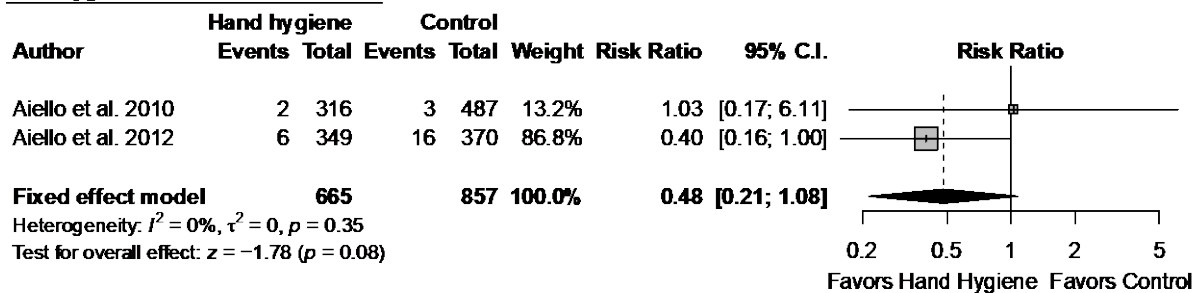


Appendix Figure 5. Metaanalysis of risk ratios for the effect of hand hygiene with or without face mask use on laboratory-confirmed influenza in elementary school setting.

Hand hygiene and facemask



Hand hygiene with or without facemask



Appendix Figure 6. Metaanalysis of risk ratios for the effect of hand hygiene with or without face mask use on laboratory-confirmed influenza in university residence hall setting.

Appendix Table 4. Summary of studies included in the review of hand hygiene

Study	Study design	Study period	Population and setting	Transmission mode	Intervention	Outcome and finding
Azman AS, 2013 (8)	Cluster-RCT School level	Nov 2007–Apr 2008	3,360 students recruited from 10 elementary schools (Pittsburgh, USA)	Primary and secondary	Hand sanitizer, soap and education; control: receive no hand hygiene training	Primary transmission outcome refers to Stebbins, S. 2011 (9); no significant difference in secondary influenza-like-illness (ILI) attack rate between intervention group and control group
Levy JW, 2014 (10)	Cluster-RCT Household level	Jun 2009–Nov 2010	191 households with index children recruited from a public pediatric hospital (Bangkok, Thailand)	Secondary	Handwashing; handwashing and face mask ; control: receive no intervention	Fewer secondary influenza infections in households in the intervention group than control group, but not statistically significant; handwashing reduces surface influenza RNA contamination
Ram PK, 2015 (14)	Cluster-RCT Household level	Jan 2009–Dec 2010	384 households with index case-patients recruited from a hospital, among them, 60 index cases were laboratory-confirmed influenza infection (Kishoregoni, Bangladesh)	Secondary	Handwashing with soap and education; control: standard practice, no handwashing education	Handwashing promotion did not effectively prevent secondary influenza infection in household setting
Aiello AE, 2010 (18)	Cluster-RCT University residence hall level	Nov 2006–Mar 2007	1,437 university hall residents from 7 halls recruited, 1,297 residents were further analyzed (Michigan, USA)	Primary	Hand sanitizer, face mask and education; face mask and education; control: receive same education, but no additional intervention	The protective effect of interventions in reducing laboratory-confirmed influenza is not significant, but the interventions may be effective in ILI reduction
Aiello AE, 2012 (19)	Cluster-RCT University residence hall level	Nov 2007–Mar 2008	1,178 university hall residents recruited from 5 halls, 1,111 residents were further analyzed (Michigan, USA)	Primary	Hand sanitizer, face mask and education; face mask and education; control: receive same education, but no additional intervention	Reductions in the rates of influenza in the intervention groups, but results were statistically insignificant; combined intervention showed significant reduction in the rates of ILI
Cowling BJ, 2008 (12)	Cluster-RCT Household level	Feb 2007–Sep 2007	198 laboratory-confirmed influenza cases and their household contacts recruited from outpatient clinics (Hong Kong, China)	Secondary	Hand sanitizer and education; face mask and education; control: received same education but no additional interventions	No significant difference between intervention groups and control group in laboratory-confirmed influenza and clinical secondary attack rate
Cowling BJ, 2009 (11)	Cluster-RCT Household level	Jan 2008–Sep 2008	407 laboratory-confirmed influenza cases recruited from outpatient clinics, 259 households which included 794 household contacts were further analyzed (Hong Kong, China)	Secondary	Hand sanitizer and education; hand sanitizer, face mask and education; control: received same education but no additional interventions	Interventions prevent influenza transmission, but results were not statistically significant; combined intervention significantly reduce influenza transmission if implement within 36 h of symptom onset among index cases
Larson EL, 2010 (13)	Cluster-RCT Household level	Nov 2006–Jul 2008	617 households recruited, 509 households were further analyzed (New York, USA)	Primary	Hand sanitizer and education; hand sanitizer, face mask and education; control: receive same education,	No significant protective effect was detected of hand hygiene, or hand hygiene and face mask interventions on influenza prevention

Study	Study design	Study period	Population and setting	Transmission mode	Intervention	Outcome and finding
Simmerman JM, 2011 (15)	Cluster-RCT Household level	Apr 2008–Aug 2009	465 households recruited from a public pediatric hospital, 442 households were further analyzed (Bangkok, Thailand)	Secondary	Handwashing; but no additional intervention Handwashing and face mask ; control: received education that was unrelated to personal protective measures, but no additional interventions	Hand hygiene and face mask interventions did not reduce influenza transmission
Stebbins S, 2011 (9)	Cluster-RCT School level	Nov 2007–Apr 2008	3360 students recruited from 10 elementary schools (Pittsburgh, USA)	Primary	Hand sanitizer, soap and education; control: receive no hand hygiene training	“WHACK the Flu” programme did not reduce laboratory-confirmed influenza infection, but reduction of absence episodes and laboratory-confirmed influenza A infection was observed
Suess T, 2011 (16)	Cluster-RCT Household level	Nov 2009–Jan 2010 and Jan 2011–Apr 2011	84 laboratory-confirmed influenza cases and 218 household contacts recruited by general practitioners or pediatricians (Berlin, Germany)	Secondary	Hand sanitizer, face mask and infection prevention material; face mask and infection prevention material; control: receive same infection prevention material, but no additional intervention	The interventions could reduce influenza transmission in household setting if implemented early and used properly
Talaat M, 2011 (17)	Cluster-RCT School level	Feb 2008–May 2008	44,451 students recruited from 60 elementary schools (Cairo, Egypt)	Primary	Handwashing; control: receive no intervention	Hand hygiene campaign effectively reduced different kinds of infectious diseases, including laboratory-confirmed influenza

Appendix Table 5. GRADE quality assessment for hand hygiene

Quality assessment						No. patients		Effect			
No. of studies	Design	Risk for bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hand hygiene with or without face mask versus control		Risk ratio	Quality	Importance
10	Randomized trial ^{1,2}	No serious risk for bias ³⁻⁷	Serious inconsistency ⁸	Serious indirectness ⁹	No serious imprecision ¹⁰	None	434/6478 (6.7%)	504/5392 (9.3%)	Risk ratio cannot be generated because of high heterogeneity	Low	Important

¹All studies were randomized trials.

²All studies were cluster-RCTs: six studies at household level, two studies at school level and two studies at university residence level.

³Five studies reported blinding of study staff including clinical staff, laboratory staff or recruiting physicians. Subjects of all studies were not blinded due to the nature of the study design.

⁴Three studies used block randomization and seven studies used simple randomization.

⁵Allocation concealment was adequate in all trials. Nine studies described the baseline characteristics of participants in all intervention groups. No serious baseline imbalance was observed.

⁶All studies reported the number of loss to follow-up in all intervention groups. No serious differential loss to follow-up occurred for whole clusters or individuals in a cluster.

⁷All studies adjusted for clustering in their analysis.

⁸High heterogeneity was observed in the pooled analysis ($I^2 > 50\%$).

⁹Studies evaluating the combined intervention were included.

¹⁰Total sample size is sufficient for a single adequately powered study.

Respiratory Etiquette

Terminology

Relevant terminology relating to respiratory etiquette is shown as follows (Appendix Table 6):

Appendix Table 6. Definition of terms relevant to respiratory etiquette

Term	Definition
Respiratory etiquette	Respiratory etiquette is also known as 'cough etiquette' (20). It is a simple hygiene practice to prevent person-to-person transmission of respiratory infections. Measures include (21): <ol style="list-style-type: none">1. Cover the mouth and nose with a tissue or mask when coughing or sneezing2. Dispose the used tissue or mask in the nearest waste basket immediately3. Proper hand hygiene after touching respiratory secretions and/or contaminated objects

Search Strategy

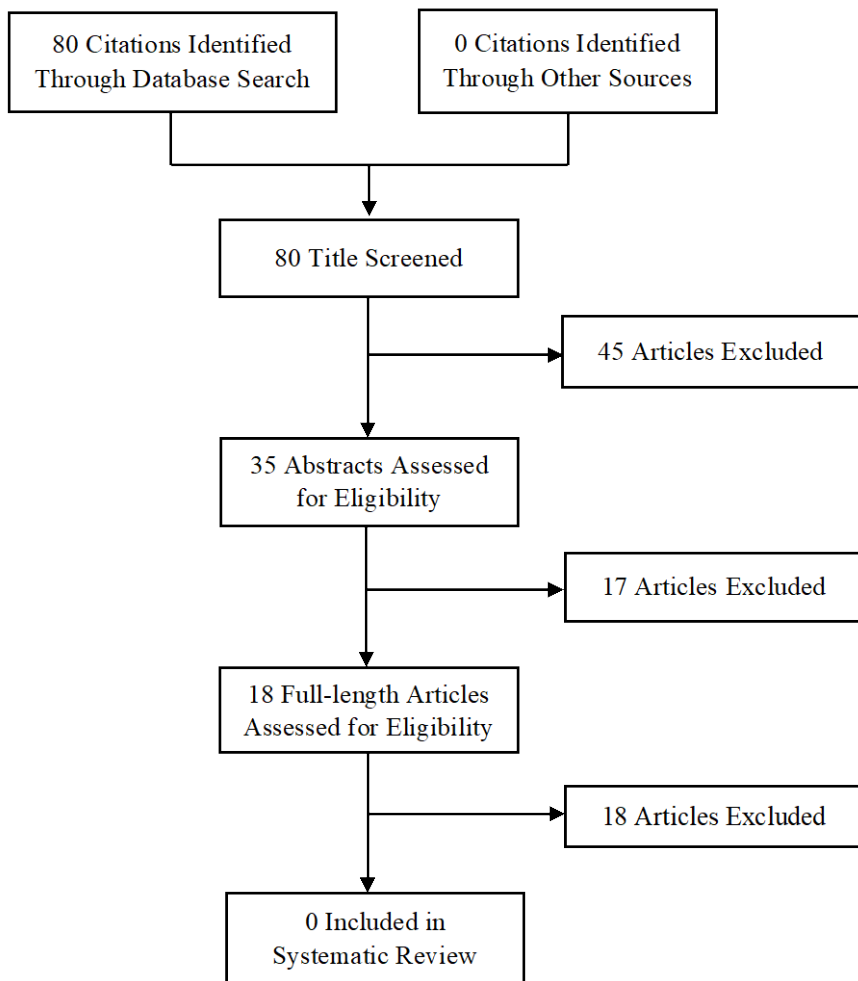
We conducted a literature search on 6 November 2018 using the following search terms (Appendix Table 7) in 4 databases (PubMed, Medline, EMBASE, and CENTRAL) to identify literatures that were available from 1946 through November 5, 2018. Studies were selected if they investigated specifically the use of respiratory/cough etiquette as the intervention along with the study outcome of laboratory-confirmed influenza virus infection. Studies that reported use of face mask as part of the respiratory etiquette were excluded because they will be covered in the next section. We reviewed literatures of all languages. Two reviewers (E.S. and S.G.) reviewed retrieved titles and subsequent relevant abstracts independently. Titles and abstract selected by any of the reviewers were included for subsequent screening. Both reviewers reviewed full-text and extracted data for selected studies independently. If a consensus was not reached, further discussion was held or opinion was obtained from a third reviewer.

Appendix Table 7. Search strategy for respiratory etiquette

Search terms	Search date	Reviewers
#1: "respiratory hygiene" OR "cough etiquette" OR "respiratory etiquette"	November 6, 2018	E.S., H.G.
#2: "influenza" OR "flu"		
#3: #1 AND #2		

Findings

Eighty articles were retrieved from 4 electronic databases after removing duplicate publications. A total of 35 abstracts were selected for screening and 18 full-text articles were assessed for eligibility. No studies were identified for this review to quantify the efficacy of respiratory etiquette with the outcome of laboratory-confirmed influenza. The flowchart is shown in Appendix Figure 7.



Appendix Figure 7. Flowchart of literature search and study selection for respiratory etiquette.

Face Masks

Terminology

Relevant terminology relating to face masks are shown as follows (Appendix Table 8):

Appendix Table 8. Definition of terms relevant to face masks

Types of masks	Terminology
Clothing, scarf, or rags tied over the nose and mouth	These are referred as alternative barriers to face mask s, but there is insufficient information available on their effectiveness on disease prevention (22).
Cloth mask	Cloth masks can be referred to “reusable masks made of cloth or any other fabric, including cotton, silk or muslin” (23). Filtration capacity is determined by the fitness of fabric and number of layers of a cloth mask (23). Cloth masks should be cleaned with household detergent thoroughly between each use (24).
Face mask	A face mask , also known as surgical, isolation, dental or medical procedure masks, is a loose-fitting, single-use disposable device that covers the mouth and nose of the user, and helps block large-particle droplets, splashes, sprays or splatter that may contain infectious agents (25). Face mask s may also help reduce exposure of user’s saliva and respiratory secretions to others (25). They are not designed to protect against breathing in small-particle aerosols that may contain viruses.
Respirator	Respirator, also known as filtering facepiece respirator (FFR), is a personal protective device that covers the nose and mouth of the user, and helps reduce the risk for inhaling hazardous airborne particles (including dust particles and infectious agents), gases, or vapors on the user (26).

Types of masks	Terminology
	The National Institute for Occupational Safety and Health (NIOSH) in the United States certifies N, R and P series particulate filtering respirator types 95, 99 and 100 with minimum filtration efficiencies of 95, 99 and 99.97%, respectively. This certification is recognized by countries such as Canada, Mexico, and Chile. In Europe, respirators marked with 'Conformité Européen' (CE) such as FFP1 (class P1), FFP2 (class P2) and FFP3 (class P3) types meet minimum filtration efficiencies of 80, 94 and 99%, respectively (27).

Search Strategy

We conducted a literature search on July 28, 2018 by using the following search terms (Appendix Table 9) in 4 databases (PubMed, Medline, EMBASE, and CENTRAL) to identify literatures that were available from 1946 through July 26, 2018. Studies were selected if they were conducted in randomized controlled trial in community settings, such as households and schools, evaluated the use of face masks with or without the combination of other intervention as 1 intervention and included the incidence of laboratory-confirmed influenza case as a study outcome. We reviewed literatures of all languages. Two reviewers (E.S. and J.X.) reviewed retrieved titles and subsequent relevant abstracts independently. Titles and abstract selected by any of the reviewers were included for subsequent screening. Both reviewers reviewed full-text and extracted data for selected studies independently. If a consensus was not reached, further discussion was held or opinion was obtained from a third reviewer.

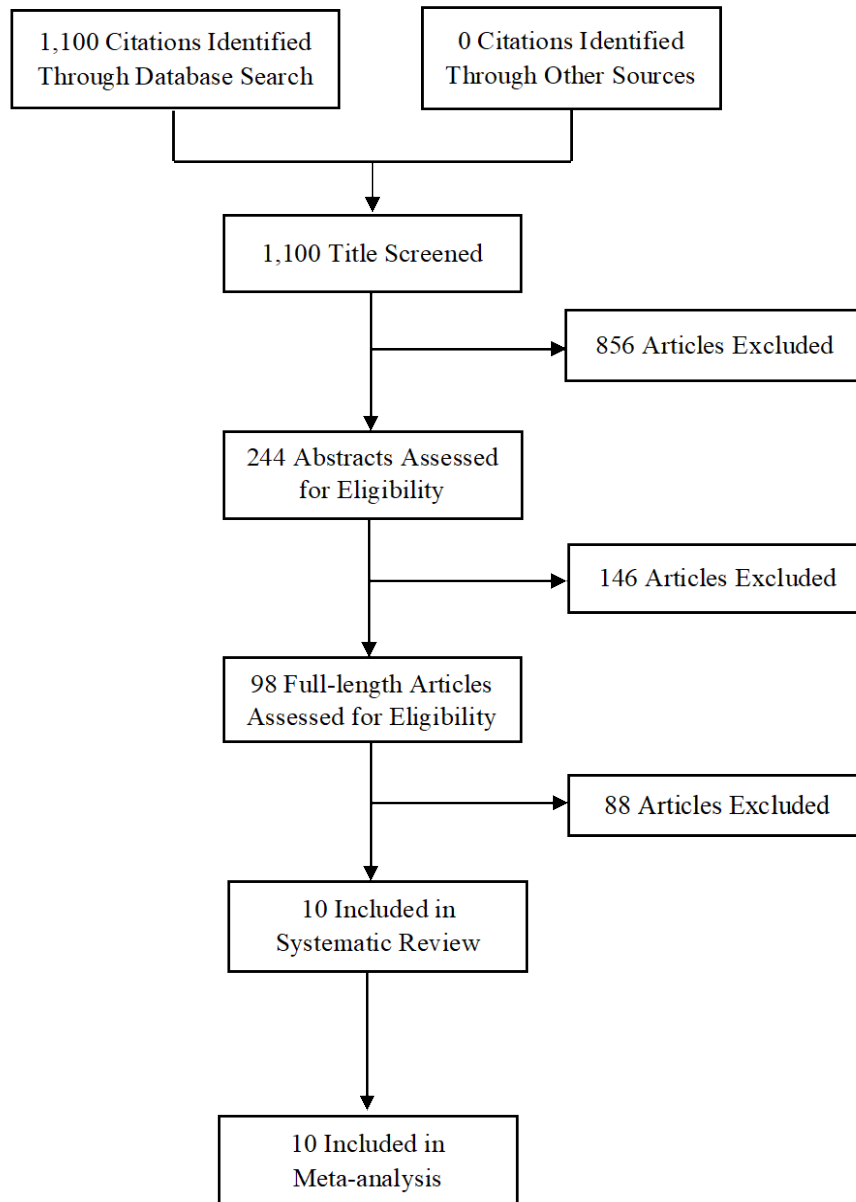
Appendix Table 9. Search strategy for face masks

Search terms	Search date	Reviewers
#1: "face mask " OR "face masks" OR "mask" OR "masks" OR "respirator" OR "respirators"	July 28, 2018	E.S., J.X.
#2: "influenza" OR "flu"		
#3: #1 AND 2		

Findings

A total of 1,100 articles were retrieved from four electronic databases after removing duplicate records. Ten relevant studies were identified for this review and metaanalysis to quantify the efficacy of community-based use of face mask s after excluding 89 articles by full-text assessment (Appendix Table 10). The flowchart is shown in Appendix Figure 8.

A total of 7/10 studies were conducted in household settings (11–13,15,16,28,29), with 2 studies conducted in university residential halls (18,19), and 1 study was conducted in Hajj pilgrims (28). Nearly half of the studies evaluated the effect of face mask use with the practice of hand hygiene, therefore results were analyzed in 2 groups 1) comparison of control group with intervention group of face mask use only, and 2) comparison of control group with intervention group of face mask use with or without hand hygiene (Appendix Figure 9).



Appendix Figure 8. Flowchart of literature search and study selection for face masks.

Among the 10 selected studies, two studies by MacIntyre et al. had a slightly different study design. One study enrolled families in which one person had laboratory-confirmed influenza, and only required the household contacts to wear face masks or P2 masks (equivalent to a N95 respirator) (28), whereas another study required only the ill members to wear face masks to evaluate the protective effect of face mask if worn by the ill individual (i.e., source control) (29). In the remaining 8 studies, every participant in the face mask intervention group was supposed to wear a face mask.

MacIntyre et al. compared the protective effect of face mask and P2 mask but they found no significant difference in ILI and laboratory-confirmed respiratory infections (influenza A and B virus, RSV, hMPV, adenovirus, PIV, coronavirus, rhinovirus, enterovirus, picornavirus); however, they reported a significant reduction in ILI if the mask was worn with good compliance in a secondary analysis (28).

Two studies by Aiello et al. were conducted in residential hall settings evaluating the effectiveness of face masks as a primary protection (18,19). They randomized university residents by cluster (each residential hall forming a cluster unit) to face masks, enhanced hand hygiene, or both. They then measured the incidence of laboratory-confirmed influenza in students in each hall. They reported no significant difference in ILI and laboratory-confirmed influenza in these three randomized groups; however, they observed a significant reduction in ILI in the combined face mask and hand hygiene intervention group during the latter half of the study period in a secondary analysis.

Seven studies were conducted in household settings where a person with laboratory-confirmed influenza was recruited as a household index case and the rate of secondary infections in the education group (control), mask group or hand hygiene group was monitored for illnesses and infections (11–13,15,16,28,29). All studies found no significant differences in the rate of laboratory-confirmed influenza virus infections in contacts in the face mask arms, and some studies reported that low compliance of the use of NPIs could affect the results (13). One study reported a significant reduction in laboratory-confirmed influenza virus infections in contacts in the face mask and hand hygiene group in the subset of households where the intervention was applied within 36 hours of symptom onset in the index case (16).

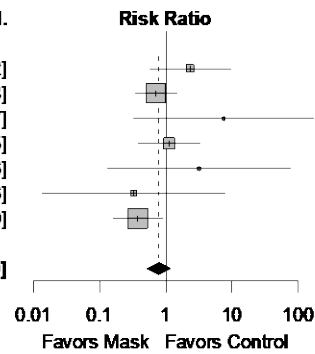
Ten studies were pooled to conduct a metaanalysis to quantify the efficacy of community-based use of face masks in the reduction of laboratory-confirmed influenza virus infection (11–13,15–19,28–30). In the pooled analysis, there was a nonsignificant RR reduction of 22% (RR 0.78, 95% CI 0.51–1.20; $I^2 = 30%$, $p = 0.25$) in the face mask group and 8% in the face mask group regardless of the enhanced hand hygiene (RR 0.92, 95% CI 0.75–1.12; $I^2 = 30%$, $p = 0.40$) (Appendix Figure 9).

Appendix Table 11 shows the results of quality assessment of evidence on face mask intervention by using the GRADE approach.

Mask only

Author	Mask		Control		Weight	Risk Ratio	95% C.I.
	Events	Total	Events	Total			
Aiello et al. 2010	5	347	3	487	5.7%	2.34	[0.56; 9.72]
Aiello et al. 2012	12	392	16	370	37.3%	0.71	[0.34; 1.48]
Barasheed et al. 2014	1	11	0	28	0.7%	7.43	[0.33; 169.47]
Cowling et al. 2008	4	61	12	205	12.5%	1.12	[0.37; 3.35]
MacIntyre et al. 2009	1	94	0	100	1.1%	3.19	[0.13; 77.36]
MacIntyre et al. 2016	0	302	1	295	3.4%	0.33	[0.01; 7.96]
Suess et al. 2012	6	69	19	82	39.4%	0.38	[0.16; 0.89]
Fixed effect model	1276		1567		100.0%	0.78	[0.51; 1.20]

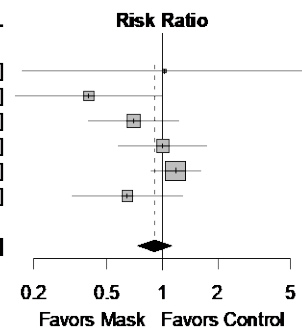
Heterogeneity: $I^2 = 30\%$, $\tau^2 = 0.1899$, $p = 0.20$
 Test for overall effect: $z = -1.15$ ($p = 0.25$)



Facemask and hand hygiene

Author	Mask		Control		Weight	Risk Ratio	95% C.I.
	Events	Total	Events	Total			
Aiello et al. 2010	2	316	3	487	1.6%	1.03	[0.17; 6.11]
Aiello et al. 2012	6	349	16	370	10.8%	0.40	[0.16; 1.00]
Cowling et al. 2009	18	258	28	279	18.8%	0.70	[0.39; 1.23]
Larson et al. 2010	25	938	24	904	17.1%	1.00	[0.58; 1.74]
Simmerman et al. 2011	66	291	58	302	39.7%	1.18	[0.86; 1.62]
Suess et al. 2012	10	67	19	82	11.9%	0.64	[0.32; 1.29]
Fixed effect model	2219		2424		100.0%	0.91	[0.73; 1.13]

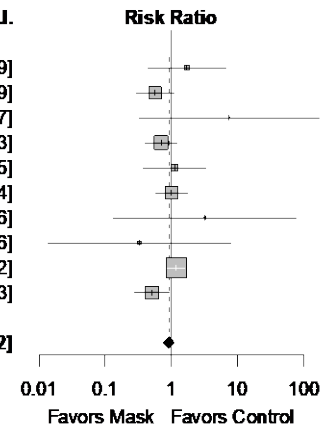
Heterogeneity: $I^2 = 35\%$, $\tau^2 = 0.0511$, $p = 0.17$
 Test for overall effect: $z = -0.85$ ($p = 0.39$)



Facemask with or without hand hygiene

Author	Mask		Control		Weight	Risk Ratio	95% C.I.
	Events	Total	Events	Total			
Aiello et al. 2010	7	663	3	487	2.1%	1.71	[0.45; 6.59]
Aiello et al. 2012	18	741	16	370	13.0%	0.56	[0.29; 1.09]
Barasheed et al. 2014	1	11	0	28	0.2%	7.43	[0.33; 169.47]
Cowling et al. 2009	18	258	28	279	16.3%	0.70	[0.39; 1.23]
Cowling et al. 2008	4	61	12	205	3.3%	1.12	[0.37; 3.35]
Larson et al. 2010	25	938	24	904	14.9%	1.00	[0.58; 1.74]
MacIntyre et al. 2009	1	94	0	100	0.3%	3.19	[0.13; 77.36]
MacIntyre et al. 2016	0	302	1	295	0.9%	0.33	[0.01; 7.96]
Simmerman et al. 2011	66	291	58	302	34.6%	1.18	[0.86; 1.62]
Suess et al. 2012	16	136	19	82	14.4%	0.51	[0.28; 0.93]
Fixed effect model	3495		3052		100.0%	0.92	[0.75; 1.12]

Heterogeneity: $I^2 = 30\%$, $\tau^2 = 0.0593$, $p = 0.17$
 Test for overall effect: $z = -0.84$ ($p = 0.40$)



Appendix Figure 9. Metaanalysis of risk ratios for the effect of face mask use with or without enhanced hand hygiene on laboratory-confirmed influenza.

Appendix Table 10. Summary of studies included in the review of face masks

Study	Study design	Study period	Population and setting	Intervention	Outcome and finding
Aiello AE, 2010 (18)	Cluster-RCT University residence hall level	Nov 2006–Mar 2007	1437 university hall residents recruited, 1297 residents were further analyzed (Michigan, USA)	Hand sanitizer and face mask and education; face mask and education; control received the same education because all intervention groups but no additional interventions were given	Significant reduction in ILI in the latter half of the study period in mask and hand hygiene group compared with the control but no significant reduction in ILI in mask and hand group or mask-only group or control
Aiello AE, 2012(19)	Cluster-RCT University residence hall level	Nov 2007–Mar 2008	1,178 university hall residents recruited from 5 halls, 1,111 residents were further analyzed (Michigan, USA)	Hand sanitizer and face mask and education; face mask and education; control received the same education because all intervention groups but no additional interventions were given	No significant reduction in rates of laboratory-confirmed influenza in mask and hand group or mask-only group or control group
Barasheed O, 2014 (30)	Cluster-RCT Hajj pilgrimage	Nov 2011–Nov 2011	164 Australian pilgrims recruited from 2011 Hajj (Saudi Arabia)	Face mask; control were not provided with face masks during the study period	No significant difference in laboratory-confirmed influenza between control and mask-only group but protective effect was observed against syndromic ILI in mask-only group compared with the control (31% vs. 53%, $p = 0.04$)
Cowling BJ, 2008 (12)	Cluster-RCT Household level	Feb 2007–Sep 2007	198 laboratory-confirmed influenza cases and their household contacts recruited from outpatient clinics (Hong Kong, China)	Hand sanitizer and education; face mask and education; control received same education because all intervention groups but no additional interventions were given	No significant reduction in the secondary influenza attack rate in control, mask or hand group
Cowling BJ, 2009 (11)	Cluster-RCT Household level	Jan 2008–Sep 2008	407 laboratory-confirmed influenza cases recruited from outpatient clinics, 259 households which included 794 household contacts were further analyzed (Hong Kong, China)	Hand sanitizer and education; hand sanitizer, face mask and education; control received same education because all intervention groups but no additional interventions were given	No significant difference in rates of laboratory-confirmed influenza in control, hand-only or mask and hand group
Larson EL, 2010 (13)	Cluster-RCT Household level	Nov 2006–Jul 2008	617 households recruited, 509 households were further analyzed (New York, NY, USA)	Hand sanitizer and education; hand sanitizer, face mask and education; control received same education because all intervention groups but no additional interventions were given	No significant reduction in rates of laboratory-confirmed influenza in control, hand-only, mask or hand group
MacIntyre CR, 2009 (28)	Cluster-RCT Household level	Aug 2006–Oct 2006 and Jun 2007–Oct 2007	145 laboratory-confirmed influenza cases and their adult household contacts recruited from a pediatric health service (Sydney, Australia)	Surgical mask; P2 mask; control were not provided with any masks during the study period	No significant difference in rate of laboratory confirmed influenza in control, face mask-only or P2 mask-only group
MacIntyre CR, 2016 (29)	Cluster-RCT Household level	Nov 2013–Jan 2014	245 ILI cases and 597 household contacts recruited from fever clinics	Face mask; control were not provided with any masks during the study period	Clinical respiratory illness, ILI and laboratory-confirmed viral infections were lower in the mask-only group

Study	Study design	Study period	Population and setting	Intervention	Outcome and finding
			(Beijing, China)		compared with the control group, but results were not statistically significant
Simmerman JM, 2011) (15)	Cluster-RCT Household level	Apr 2008–Aug 2009	465 households recruited from a public pediatric hospital, 442 households were further analyzed (Bangkok, Thailand)	Handwashing; handwashing and face mask; control received education that was unrelated to personal protective measures and no additional interventions were given	No significant reduction in rate of secondary influenza infection in control, hand-only, mask or hand group
Suess (2012) (16)	Cluster-RCT Household level	Nov 2009–Jan 2010 and Jan 2011–Apr 2011	84 laboratory-confirmed influenza cases and 218 household contacts recruited by general practitioners or pediatricians (Berlin, Germany)	Hand sanitizer and face mask; face mask; control were not provided with any face masks nor hand-rub during the study period	No significant difference in rate of laboratory confirmed influenza in control, mask-only, mask or hand group

Appendix Table 11. GRADE quality assessment for face masks

Quality assessment						No. of patients		Effect		
No. studies	Design	Risk for bias	Inconsistency	Indirectness	Imprecision	Other considerations	Face mask with or without hand hygiene versus control	Risk ratio (95% CI)	Quality	Importance
10	Randomized trial ^{1,2}	No serious risk for bias ³⁻⁷	Serious inconsistency ⁸	Serious indirectness ⁹	No serious imprecision ¹⁰	None	156/3495 161/3052	0.92 (0.75–1.12)	Low	Important

¹All studies were randomized trials.

²All studies were cluster-RCTs: two studies at university residence level, seven studies at household level and one study randomized by sleeping tent during Hajj pilgrim.

³Eight studies reported blinding of study staffs including clinical staff, laboratory staff or recruiting physicians. Subjects of all studies were not blinded.

⁴Three studies used block randomization; six studies used computer program to generate the randomization order and one study used ticket-picking for selection.

⁵Allocation concealment was adequate in all trials. Eight studies described the baseline characteristics of participants in all intervention groups. No serious baseline imbalance was observed.

⁶All study reported the number of loss to follow-up in all intervention groups. No serious differential loss to follow-up occurred for whole clusters or persons in a cluster.

⁷Seven studies adjusted for clustering in their analysis.

⁸Moderate heterogeneity was observed in the pooled analysis.

⁹Studies evaluating the combined intervention were included.

¹⁰Total sample size is insufficient in the pooled analysis.

Surface and Object Cleaning

Terminology

Relevant terminology relating to surface and object cleaning is shown as follows (Appendix Table 12):

Appendix Table 12. Definition of terms relevant to surface and object cleaning

Term	Definition
Surface and object cleaning	Routine cleaning of frequently used surfaces and objects to reduce influenza transmission.

Search Strategy

We conducted a literature search on October 15, 2018 by using the following search terms (Appendix Table 13) in 4 databases (PubMed, Medline, EMBASE, and CENTRAL) to identify literature that was available from 1946 through October 14, 2018. Study selection criteria are studies reporting the effect of surface and object cleaning intervention compared with no intervention in preventing influenza virus infections in community settings. There were no limitations on the types of cleaning techniques. Randomized controlled trials and other types of epidemiologic studies were included if they evaluated the effect of surface and object cleaning on laboratory-confirmed influenza, ILI or respiratory illness. Simulation studies, recommendations, and commentaries/editorials were excluded. We reviewed literatures of all languages. Two reviewers (J.X. and E.S.) reviewed retrieved titles and subsequent relevant abstracts independently. Titles and abstract selected by any of the reviewers were included for subsequent screening. Both reviewers reviewed full-text and extracted data for selected studies independently. If a consensus was not reached, further discussion was held or opinion was obtained from a third reviewer.

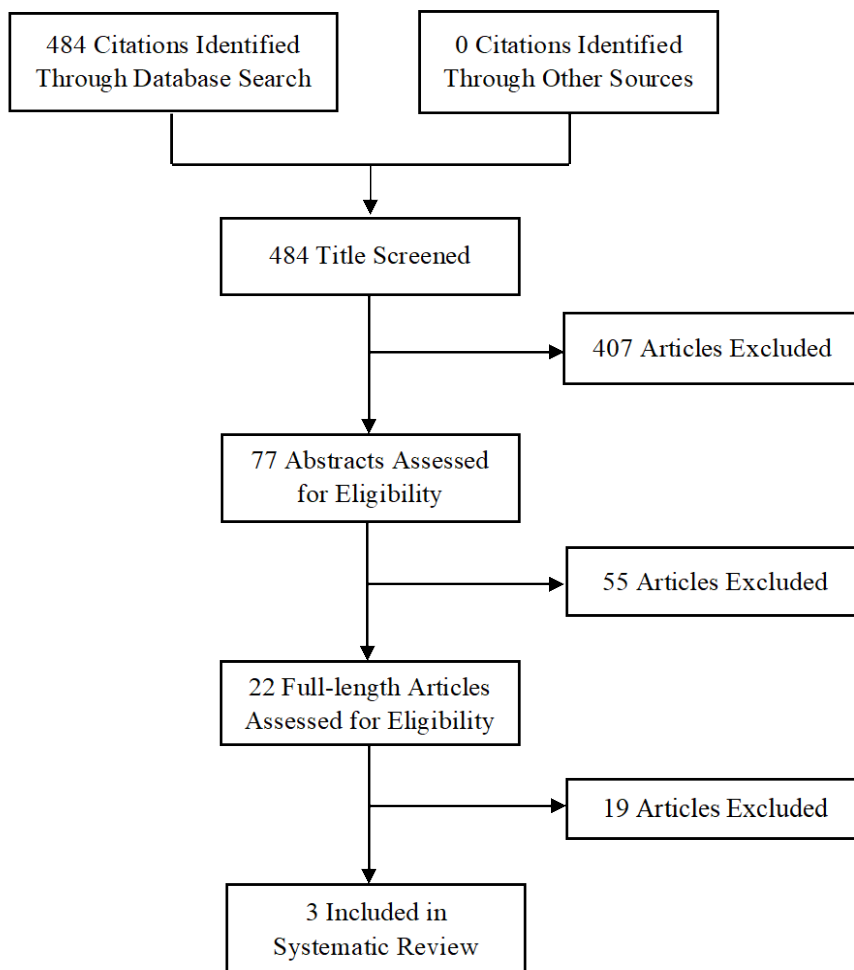
Appendix Table 13. Search strategy for surface and object cleaning

Search terms	Search date	Reviewers
#1: "surface" OR "surfaces" OR "object" OR "objects" OR "fomite" OR "fomites" OR "environment" OR "environmental"	October 15, 2018	J.X., E.S.
#2: "clean" OR "cleans" OR "cleaning" OR "cleanse" OR "cleansing" OR "disinfect" OR "disinfects" OR "disinfection" OR "disinfecting" OR "wipe" OR "wipes" OR "sanitize" OR "sanitizes" OR "sanitizing" OR "sanitation" OR "sterilize" OR "sterilizes" OR "sterilizing" OR "sterilization" OR "sterilise" OR "sterilises" OR "sterilising" OR "sterilisation" OR "decontaminate" OR "decontaminates" OR "decontaminating" OR "decontamination"		
#3: "influenza" OR "flu"		
#4: #1 AND #2 AND #3		

Findings

We identified 484 reviews through the search, of which 462 reviews were removed during title and abstract screening. We further excluded 19 articles after full text assessment because

they did not specify the surface or object cleaning as the study intervention or respiratory infections as the study outcome. Three articles were included in the systematic review to study the effectiveness of surface and object cleaning to prevent influenza infection. The flowchart is shown in Appendix Figure 10.



Appendix Figure 10. Flowchart of literature search and study selection for surface and object cleaning.

A cross-sectional study showed that bleach use in households was associated with a statistically significant increase in self-reported influenza based on self-administered questionnaires. The authors, however, did not specify the definition of influenza illness and they also hypothesized that the increase of cases might be due to the immunosuppressive properties of bleach (31). A randomized controlled trial with disinfection of toys and linen in day care nurseries reported a reduction in the detections of viruses in the environment, but no significant

reduction was observed on influenza-related and other acute respiratory-related illnesses among children (32). Another randomized controlled trial conducted in elementary schools demonstrated that hand hygiene with alcohol-based hand sanitizer and surface disinfection with quaternary ammonium wipes intervention could reduce gastrointestinal illness absenteeism, but not respiratory illness absenteeism (32). Detailed study description is shown in Appendix Table 14.

Appendix Table 14. Summary of studies included in the review of surface and object cleaning

Study	Study design	Study period	Population and setting	Intervention	Outcome measures	Main findings
Casas L, 2015 (30)	Cross-sectional study	Apr 2008–Dec 2010	9,102 students from schools (Spain, Netherlands and Finland)	Not intervention. Environment cleaning with bleach versus no use of bleach	Self-reported influenza	Passive contact with cleaning bleach in the household might increase the risk for respiratory and other infections in children, which might have an adverse effect on school-age children's health
Ibelfelt T, 2015 (31)	Cluster-RCT	Autumn 2012–Apr 2013	12 d-care nurseries caring for 587 children (Copenhagen, Denmark)	Disinfection of toys; control: receive no intervention	Respiratory infections and surface sample influenza virus detection	Frequent disinfection of toys could reduce the presence of environmental microbial, but not significantly reduce respiratory illness of nursery children
Sandora TJ, 2008 (32)	Cluster-RCT	Mar 2006–May 2006	285 students from elementary schools (Ohio, USA)	Hand hygiene and surface cleaning; control: usual baseline practice, no additional intervention	Respiratory illness	Surface disinfection could reduce gastrointestinal-related absenteeism among school-age children, but not respiratory-related illness

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