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Effectiveness of N95 respirators versus surgical masks against influenza: A systematic review and meta-analysis

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Abstract

Objective: Previous meta-analyses concluded that there was insufficient evidence to determine the effect of N95 respirators. We aimed to assess the effectiveness of N95 respirators versus surgical masks for prevention of influenza by collecting randomized controlled trials (RCTs).

Methods: We searched PubMed, EMbase and The Cochrane Library from the inception to January 27, 2020 to identify relevant systematic reviews. The RCTs included in systematic reviews were identified. Then we searched the latest published RCTs from the above three databases and searched ClinicalTrials.gov for unpublished RCTs. Two reviewers independently extracted the data and assessed risk of bias. Meta-analyses were conducted to calculate pooled estimates by using RevMan 5.3 software.

Results: A total of six RCTs involving 9 171 participants were included. There were no statistically significant differences in preventing laboratory-confirmed influenza (RR = 1.09, 95% CI 0.92-1.28, P > .05), laboratory-confirmed respiratory viral infections (RR = 0.89, 95% CI 0.70-1.11), laboratory-confirmed respiratory infection (RR = 0.74, 95% CI 0.42-1.29) and influenzalike illness (RR = 0.61, 95% CI 0.33-1.14) using N95 respirators and surgical masks. Meta-analysis indicated a protective effect of N95 respirators against laboratory-confirmed bacterial colonization (RR = 0.58, 95% CI 0.43-0.78).

Conclusion: The use of N95 respirators compared with surgical masks is not associated with a lower risk of laboratory-confirmed influenza. It suggests that N95 respirators should not be recommended for general public and nonhigh-risk medical staff those are not in close contact with influenza patients or suspected patients.

KEYWORDS

influenza, masks, N95 respirator, respiratory protective devices, respiratory tract infections, surgical mask

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have mortality rates about 10% and 37%, respectively. Since the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), facemasks have been considered to be vitally important to reduce the risk of infection because vaccination or specific anti-infective treatments are

unavailable.^{2,3} N95 respirators are used to prevent users from inhaling small airborne particles and must fit tightly to the user's face. Surgical masks are designed to protect wearers from microorganism transmission and fit loosely to the user's face.^{5,6} Although surgical masks cannot prevent inhalation of small airborne particles, both of them can protect users from large droplets and sprays.^{7,8}

There are conflicting recommendations for severe acute respiratory syndrome (SARS) and pandemic influenza: the World Health

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Organization (WHO) recommends using masks in low-risk situations and respirators in high-risk situations, but the Centers for Disease Control and Prevention (CDC) recommends using respirators in both low and high-risk situations. However, N95 respirators may play a limited role in low-resource settings, where there are a finite number of N95 respirators, or it may be unaffordable. Also, previous meta-analyses concluded there was insufficient evidence to determine the effect of N95 respirators due to a small number of studies that is prone to lack of statistical power. Additionally, these meta-analyses were limited by the small number of included randomized control trials (RCTs). More rigorous RCTs of comparing N95 respirators with surgical masks against influenza published in recent years were not included in previous meta-analyses. 12-14

In light of the growing number of RCTs of masks use for protecting against influenza, this systematic review and meta-analysis aimed to assess the effectiveness of N95 respirators versus surgical masks for prevention of influenza.

2 | METHODS

This meta-analysis was conducted based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. 15

2.1 | Inclusion and exclusion criteria

Inclusion criteria were (1) study type: RCT (including cluster-randomized trial) and nonrandomized controlled study; (2) participants: humans with influenza (including pandemic strains, seasonal influenza A or B viruses and zoonotic viruses such as swine or avian influenza), and other respiratory viral infections (as a proxy for influenza); (3) intervention and comparator: N95 respirators versus surgical masks; (4) primary outcome: laboratory-confirmed influenza; (5) secondary outcomes: laboratory-confirmed respiratory viral infections, laboratory-confirmed bacterial colonization, laboratory-confirmed respiratory infection, and influenzalike illness; and (6) settings: hospital or community. RCTs were selected due to the potential possibility of high evidence level. Exclusion criteria were (1) theoretical models; (2) human/nonhuman experimental laboratory studies; and (3) conference abstract.

2.2 | Search strategy

We searched PubMed, EMBASE, and The Cochrane Library databases from inception to January 27, 2020, to identify published systematic reviews on evaluating the use of masks for preventing influenza. Search strategy in PubMed could be found in Table 1, and the strategy was adequately adjusted to use in other databases. Then, primary RCTs included in the systematic reviews were identified. Additionally, we conducted an additional search to identify RCTs published in the past five years from January 27, 2015, to January 27, 2020, using the databases and search strategies described above. We also

TABLE 1 Search strategy in PubMed

Number	PubMed
#1	"systematic review"[Text Word]
#2	meta analysis[Publication Type]
#3	#1 OR #2
#4	masks OR respiratory protective devices[MeSH Terms]
#5	mask* OR facemask* OR N95* OR N-95*[Text Word]
#6	#4 OR #5
#7	influenza, human OR severe acute respiratory syndrome[MeSH Terms]
#8	flu OR influenza OR grippe OR SARS OR "severe acute respiratory syndrome" [Text Word]
#9	#7 OR #8
#10	#3 AND #6 AND #9

searched for ClinicalTrials.gov to obtain unpublished data. There were no publication status and language restrictions on selecting the studies.

2.3 | Study selection and data extraction

Two reviewers independently screened the articles based on the titles, abstracts and full texts. Then, two reviewers independently exacted the following data from included studies: first author, publication year, country, disease, details of study population and intervention, study design, sample size, settings, and results. All disagreements were resolved by discussion.

2.4 | Risk of bias assessment

Two reviewers independently assessed the risk of bias of the selected RCTs using the Cochrane Risk of Bias tool, ¹⁶ which includes domains on random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, and selective reporting. For each RCT, every domain was judged among 3 levels: high risk, unclear risk, and low risk. Disagreements were resolved by discussion.

2.5 | Data analysis

All statistical analyses were performed using Review Manager (RevMan) version 5.3. Comparable data from studies with similar interventions and outcomes were pooled using forest plots. Relative risk (RR) with 95% confidence intervals (CIs) for dichotomous data was used as the effect measure. Between-study heterogeneity was assessed using the I^2 for each pooled estimate. We adopted a random-effects model for heterogeneity P < .10. We performed a subgroup analysis based on the settings (hospital, community) due to the possibility of clinical heterogeneity. A sensitivity analysis was conducted to evaluate the robustness of the results by excluding individual studies for each forest plot. Funnel plots were planned to assessed publication bias. Because of the small number of studies

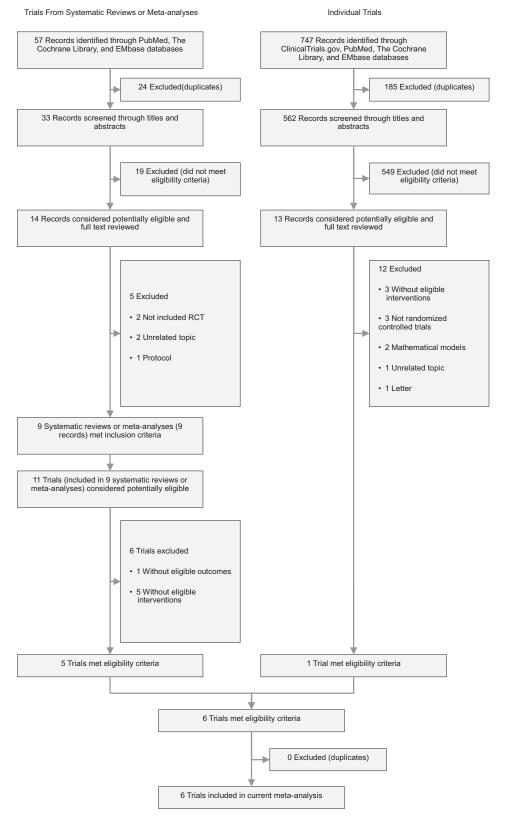


FIGURE 1 Literature search and screening process

TABLE 2 Excluded studies and reasons for exclusion

Excluded studies	Reasons for exclusion
Cowling et al 2008 ²⁶	This trial did not have eligible interventions.
Jacobs et al 2009 ²⁷	This trial did not have eligible outcomes.
Aiello et al 2010 ²⁸	This trial did not have eligible interventions.
Barasheed et al 2014 ²⁹	This trial did not have eligible interventions.
MacIntyre et al 2015 ³⁰	This trial did not have eligible interventions.
Cowling et al 2014 ³¹	This study developed mathematical models of transmission of influenza and is not a trial in the real world.
MacIntyre et al 2015 ³⁰	This trial did not have eligible interventions.
Wang et al 2015 ³²	This study is a protocol.
Ambrosch et al 2016 ³³	This is a prospective cohort study.
Chughtai et al 2016 ³⁴	This trial focused on compliance with the use of medical and cloth masks.
MacIntyre et al 2016 ¹⁴	This trial did not have eligible interventions.
Sokol et al 2016 ³⁵	This is a retrospective study.
MacIntyre et al 2017 ³⁶	This study is a pooled analysis of two trials.
Zhang et al 2018 ³⁷	This study developed mathematical models of transmission of influenza, and is not a trial in the real world.
Glatt et al 2020 ³⁸	This is a letter.
Simmerman et al 2011 ³⁹	This trial did not have eligible interventions.
Radonovich et al 2016 ¹³	This trial is duplicated.
Cowling et al 2009 ⁴⁰	This trial did not have eligible interventions.

available for each pooled estimate, we failed to assess publication bias.

come assessors were blinded. All studies had complete outcome data or described comparable numbers and reasons for withdrawal across groups and prespecified outcomes.

3 | RESULTS

3.1 | Search results and study characteristics

The details on the literature search and screening process can be found in Figure 1. Excluded studies and reasons for exclusion were shown in Table 2. In total, we included six RCTs^{12,18-22} and found no unpublished data of RCTs from ClinicalTrials.gov. The characteristics of these RCTs were presented in Table 3. The included studies published between 2009 and 2019. A total of 9171 participants in Canada, Australia, China, or America were included, and the number of participants in each RCT ranged from 435 to 5180 patients. The follow-up duration varied from 2 to 15 weeks. Five studies included participants in hospitals, ^{12,18,20-22} and one in households. ¹⁹ Because of different definitions of outcome in included studies, we redefined the laboratory-confirmed respiratory infection as respiratory influenza, other viruses or bacteria infection.

3.2 | Risk of bias

The results of the risk of bias assessment can be found in Figure 2. Five studies reported the computer-generated random sequences, while only one mentioned randomization. All studies did not mention allocation concealment. Participants and trial staff were not blinded in two studies, and the other two studies failed to mention the blinding of participants and personnel. Four studies did not report whether the out-

3.3 | Effectiveness

Five RCTs involving 8444 participants reported laboratory-confirmed influenza. $^{12,18-21}$ Meta-analysis with fixed-effects model revealed that there was no statistically significant differences in preventing influenza using N95 respirators and surgical masks (RR = 1.09, 95% CI 0.92-1.28, P > .05) (Figure 3). The results of subgroup analyses were consistent with this regardless of the hospital or the community. The results of the sensitivity analysis were not altered after excluding each trial.

Four RCTs¹⁸⁻²¹ involving 3264 participants reported laboratory-confirmed respiratory viral infections. Meta-analysis with fixed-effects model revealed that there were no statistically significant differences in preventing respiratory viral infections using N95 respirators and surgical masks (RR = 0.89, 95% CI 0.70-1.11, P > .05) (Figure 4). The results of subgroup analyses were consistent regardless of the hospital or the community. However, the sensitivity analysis after excluding the trial by Loeb et al¹⁸ showed a significant effect of N95 respirators on preventing respiratory viral infections (RR = 0.61, 95% CI 0.39-0.98, P < .05).

Two RCTs 21,22 involving 2538 participants reported laboratory-confirmed bacterial colonization. Meta-analysis with fixed-effects model revealed that compared with surgical masks, N95 respirators significantly reduced bacterial colonization in hospitals (RR = 0.58, 95% CI 0.43-0.78, P < .05) (Figure 5). The sensitivity

Study	Setting	Participants	Interventions	Outcomes	Notes
Loeb et al 2009 ¹⁸	8 hospitals in Ontario, Canada: emergency departments, acute medical units and pediatric units	446 nurses; individual-level randomization	 Intervention: targeted use, fit-tested N95 respirator Control: targeted use, surgical mask 	 Laboratory-confirmed respiratory infection, influenza-like illness, workplace absenteeism 5-week follow-up 	Noninferiority trial Detection of influenza A and B. respiratory syncytial virus metapneumovirus, parainfluenza virus, rhinovirus-enterovirus, coronavirus and adenovirus
MacIntyre et al 2009 ¹⁹	145 households in Sydney, Australia	145 index patients and 290 household contacts in 145 households; cluster randomization by household	Intervention 1: continual use, surgical mask Intervention 2: continual use, nonfit-tested N95 respirator Control: lifestyle measures	 Laboratory-confirmed respiratory virus infection, influenza-like illness 2-week follow-up 	Detection of influenza A and B, respiratory syncytial virus, parainfluenza virus, rhinovirus-enterovirus, coronavirus, adenovirus
MacIntyre et al 2011 ²⁰ /2014 ²²	15 hospitals in Beijing, China: emergency departments and respiratory wards	1441 nurses, doctors and ward clerks; cluster randomization by hospital	Intervention 1: continual use, fit-tested N95 respirator Intervention 2: continual use, nonfit-tested N95 respirator Control: continual use, surgical mask	 Laboratory-confirmed respiratory infection, influenza-like illness 5-week follow-up 	Detection of influenza A and B, respiratory syncytial virus, metapneumovirus, parainfluenza virus, rhinovirus-enterovirus, coronavirus, adenovirus, streptococcus pneumoniae, bordetella pertussis, chlamydophila pneumoniae and haemophilus influenzae type B
MacIntyre et al 2013 ²¹	19 hospitals in Beijing, China: emergency departments and respiratory wards	1669 nurses, doctors and ward clerks; cluster randomization by ward	Intervention 1: continual use, fit-tested N95 respirator Intervention 2: targeted use, fit-tested N95 respirator Control: continual use, surgical mask	 Laboratory-confirmed respiratory infection, influenza-like illness 5-week follow-up 	Detection of influenza A and B, respiratory syncytial virus metapneumovirus, parainfluenza virus, rhinovirus-enterovirus, coronavirus, adenovirus, S. pneumoniae, B. pertussis, C. pneumoniae, M. pneumoniae and H. influenzae type B
Radonovich et al 2019 ¹²	7 hospitals in US: primary care facilities, dental clinics, adult and pediatric clinics, dialysis units, urgent care facilities and emergency departments, and emergency transport services	5180 nurses/nursing trainees, clinical care support staff, administrative/clerical staff, physicians/advanced practitioners/physician trainees, registrations/clerical receptions, social workers/pastoral cares and environmental service workers/housekeepers; cluster randomization by outpatient clinic or outpatient setting	Intervention: targeted use, fit-tested N95 respirator Control: targeted use, medical mask	Laboratory-confirmed respiratory infection, laboratory-confirmed influenza, laboratory-detected respiratory illness, acute respiratory illness. 12-week follow-up	Effectiveness study Detection of influenza A and B, respiratory syncytial virus, metapneumovirus, parainfluenza virus, rhinovirus-enterovirus, coronavirus, coxsackie/echovirus

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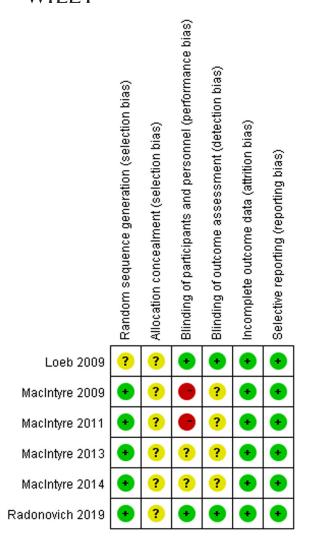


FIGURE 2 Risk of bias summary

analysis showed that the results did not change after excluding each trial.

Two RCTs^{12,22} involving 6621 participants reported laboratory-confirmed respiratory infection. Meta-analysis with random-effects model revealed that there were no statistically significant differences in preventing respiratory infection using N95 respirators and surgical masks in hospitals (RR = 0.74, 95% CI 0.42-1.29, P > .05) (Figure 6). However, the sensitivity analysis after excluding the trial by Radonovich et al¹² showed a significant effect of N95 respirators on preventing respiratory infection (RR = 0.53, 95% CI 0.35-0.82, P < .05).

Five RCTs involving 8444 participants reported influenza like illness. $^{12.18-21}$ Meta-analysis with random-effects model revealed that there were no statistically significant differences in preventing influenza like illness using N95 respirators and surgical masks (RR = 0.61, 95% CI 0.33-1.14, P > .05) (Figure 7). The results of subgroup analyses indicated that statistically significant superiority of N95 respirators over surgical masks against influenza like illness (RR = 0.37, 95% CI 0.20-0.71, P < .05) in the community (only one

RCT). The sensitivity analysis showed results remained unchanged after excluding each trial.

4 | DISCUSSION

This meta-analysis showed that there were no statistically significant differences in preventing laboratory-confirmed influenza, laboratory-confirmed respiratory viral infections, laboratory-confirmed respiratory infection and influenza-like illness using N95 respirators and surgical masks. N95 respirators provided a protective effect against laboratory-confirmed bacterial colonization. In subgroup analysis, similar results could be found in the hospital and community for laboratory-confirmed influenza and laboratory-confirmed respiratory viral infections. However, sensitivity analysis showed unstable results for the prevention of laboratory-confirmed respiratory viral infections and laboratory-confirmed respiratory viral infections and laboratory-confirmed respiratory infection.

Through the course of influenza pandemics, large numbers of face-masks may be required to use in long periods to protect people from infections. ²³ Using N95 respirators is likely to result in discomfort, for example, headaches. ²³ A previous study ³ reported that there was an inverse relationship between the level of compliance with wearing an N95 respirator and the risk of clinical respiratory illness. It is difficult to ensure high compliance due to this discomfort of N95 respirators in all studies.

The reason for the similar effects on preventing influenza for the use of N95 respirators *versus* surgical masks may be related to low compliance to N95 respirators wear,²³ which may lead to more frequent doffing compared with surgical masks.¹³ Although N95 respirators may confer superior protection in laboratory studies designing to achieve 100% intervention adherence,²⁴ the routine use of N95 respirators seems to be less acceptable due to more significant discomfort in real-world practice.¹¹ Therefore, the benefit of N95 respirators of fitting tightly to faces is offset or subjugated.¹³ However, it should be noted that the surgical masks are primarily designed to protect the environment from the wearer, whereas the respirators are supposed to protect the wearer from the environment.²⁵

There are several limitations to this study. First, some RCTs had a high risk of bias due to lack of allocation concealment and blinding; although it is impractical to blind participants who would know the type of masks they are wearing. Second, the number of included studies focusing on the community was small. Consequently, the results of the subgroup analysis might be unreliable. Third, we identified RCTs from published systematic reviews, which may result in the omission of relative RCTs. Finally, there might be publication bias, and we cannot assess it due to an insufficient number of included RCTs.

In conclusion, the current meta-analysis shows the use of N95 respirators compared with surgical masks is not associated with a lower risk of laboratory-confirmed influenza. It suggests that N95 respirators should not be recommended for the general public and nonhigh risk medical staffs those are not in close contact with influenza patients or suspected patients.

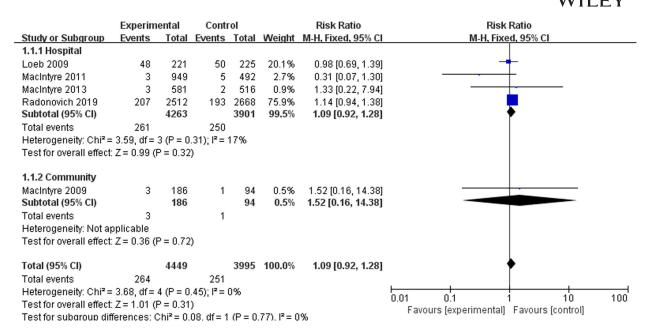


FIGURE 3 Results of meta-analysis to determine the effectiveness of N95 respirators versus surgical masks against laboratory-confirmed influenza

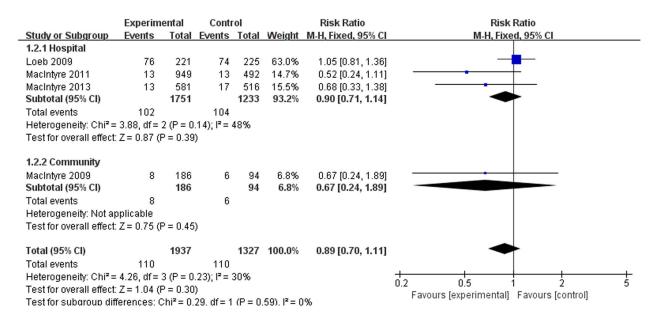


FIGURE 4 Results of meta-analysis to determine the effectiveness of N95 respirators versus surgical masks against laboratory-confirmed respiratory viral infections

	N95 respi		medical m			Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
MacIntyre 2013	36	581	52	516	50.5%	0.61 [0.41, 0.92]		
MacIntyre 2014	43	949	41	492	49.5%	0.54 [0.36, 0.82]		
Total (95% CI)		1530		1008	100.0%	0.58 [0.43, 0.78]	•	
Total events	79		93					
Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%							0.2 0.5 1 2	<u></u>
Test for overall effect:	Z= 3.68 (P	= 0.0002)				0.2 0.5 1 2 Favours [experimental] Favours [control]	5

FIGURE 5 Results of meta-analysis to determine the effectiveness of N95 respirators versus surgical masks against laboratory-confirmed bacterial colonization

	N95 respirators medical masks					Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
MacIntyre 2014	40	949	39	492	43.5%	0.53 [0.35, 0.82]	
Radonovich 2019	371	2512	417	2668	56.5%	0.94 [0.83, 1.07]	-
Total (95% CI)		3461		3160	100.0%	0.74 [0.42, 1.29]	
Total events	411		456				
Heterogeneity: Tau ² =	0.14; Chi ² =	6.37, df	0.2 0.5 1 2 5				
Test for overall effect: Z = 1.08 (P = 0.28)							
	,	,					Favours [experimental] Favours [control]

FIGURE 6 Results of meta-analysis to determine the effectiveness of N95 respirators versus surgical masks against laboratory-confirmed respiratory infection

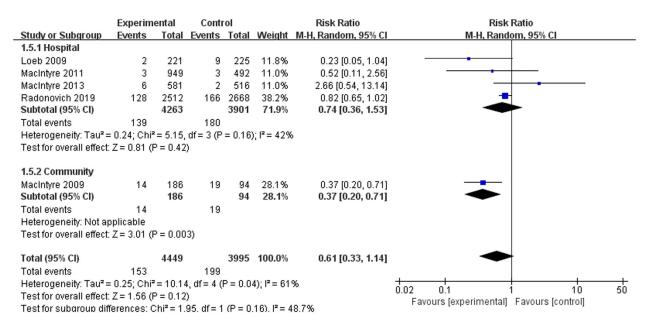


FIGURE 7 Results of meta-analysis to determine the effectiveness of N95 respirators versus surgical masks against influenzalike illness

CONFLICT OF INTEREST

None.

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