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N95 Respirators vs Medical Masks for Preventing Influenza Among Health Care Personnel
A Randomized Clinical Trial

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IMPORTANCE Clinical studies have been inconclusive about the effectiveness of N95 respirators and medical masks in preventing health care personnel (HCP) from acquiring workplace viral respiratory infections.

OBJECTIVE To compare the effect of N95 respirators vs medical masks for prevention of influenza and other viral respiratory infections among HCP.

DESIGN, SETTING, AND PARTICIPANTS A cluster randomized pragmatic effectiveness study conducted at 137 outpatient study sites at 7 US medical centers between September 2011 and May 2015, with final follow-up in June 2016. Each year for 4 years, during the 12-week period of peak viral respiratory illness, pairs of outpatient sites (clusters) within each center were matched and randomly assigned to the N95 respirator or medical mask groups.

INTERVENTIONS Overall, 1993 participants in 189 clusters were randomly assigned to wear N95 respirators (2512 HCP-seasons of observation) and 2058 in 191 clusters were randomly assigned to wear medical masks (2668 HCP-seasons) when near patients with respiratory illness.

MAIN OUTCOMES AND MEASURES The primary outcome was the incidence of laboratory-confirmed influenza. Secondary outcomes included incidence of acute respiratory illness, laboratory-detected respiratory infections, laboratory-confirmed respiratory illness, and influenzalike illness. Adherence to interventions was assessed.

RESULTS Among 2862 randomized participants (mean [SD] age, 43 [11.5] years; 2369 [82.8%]) women), 2371 completed the study and accounted for 5180 HCP-seasons. There were 207 laboratory-confirmed influenza infection events (8.2% of HCP-seasons) in the N95 respirator group and 193 (7.2% of HCP-seasons) in the medical mask group (difference, 1.0%, [95% CI, −0.5% to 2.5%]; *P* = .18) (adjusted odds ratio [OR], 1.18 [95% CI, 0.95-1.45]). There were 1556 acute respiratory illness events in the respirator group vs 1711 in the mask group (difference, −21.9 per 1000 HCP-seasons [95% CI, −48.2 to 4.4]; *P* = .10); 679 laboratory-detected respiratory infections in the respirator group vs 745 in the mask group (difference, −8.9 per 1000 HCP-seasons, [95% CI, −33.3 to 15.4]; *P* = .47); 371 laboratory-confirmed respiratory illness events in the respirator group vs 417 in the mask group (difference, −8.6 per 1000 HCP-seasons [95% CI, −28.2 to 10.9]; *P* = .39); and 128 influenzalike illness events in the respirator group vs 166 in the mask group (difference, −11.3 per 1000 HCP-seasons [95% CI, −23.8 to 1.3]; *P* = .08). In the respirator group, 89.4% of participants reported "always" or "sometimes" wearing their assigned devices vs 90.2% in the mask group.

CONCLUSIONS AND RELEVANCE Among outpatient health care personnel, N95 respirators vs medical masks as worn by participants in this trial resulted in no significant difference in the incidence of laboratory-confirmed influenza.

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Visual Abstract

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Supplemental content

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Health care personnel (HCP) who are routinely exposed to viral respiratory infections in the workplace[1] may transmit infection to others. It is widely recognized that HCP, as a group, incompletely adhere to infection prevention recommendations and practice standards. Inpatient respiratory protection studies suggest adherence rates vary from 10% to 84%.[2-4] While laboratory studies designed to achieve 100% intervention adherence have shown that N95 filtering facepiece respirators are more efficacious than medical masks at reducing exposure to aerosols,[5] comparative clinical effectiveness studies have been inconclusive.[3,4,6] Some experts argue that N95 respirators and medical masks are equivalent in clinical settings.[2,7] Pragmatic effectiveness trials are increasingly recognized as an essential component of medical evidence, in part because efficacy studies may overestimate effectiveness and true adherence.[8]

Disposable N95 respirators and medical masks are both worn by HCP for self-protection; however, these masks have different intended uses. N95 respirators are designed to prevent the wearer from inhaling small airborne particles,[9] must meet filtration requirements,[10] and fit tightly to the wearer's face, limiting facial seal leakage. Medical masks, frequently called surgical masks, are intended to prevent microorganism transmission from the wearer to the patient. Medical masks fit the face loosely and do not reliably prevent inhalation of small airborne particles. However, medical masks prevent hand-to-face contact and facial contact with large droplets and sprays.[11]

Clinical evidence is inconclusive regarding whether N95 respirators are more effective than medical masks for preventing viral respiratory infection among HCP, including influenza,[3,4,6,12] accounting for differing practices[2] and positions held by clinical,[7] public health,[13,14] and regulatory organizations.[15] The objective of this study was to compare[13] the effectiveness of N95 respirators vs medical masks worn by HCP in clinical practice for prevention of workplace-acquired influenza and other viral respiratory infections in geographically diverse, high-exposure, outpatient settings.

Key Points

Question Is the use of N95 respirators or medical masks more effective in preventing influenza infection among outpatient health care personnel in close contact with patients with suspected respiratory illness?

Findings In this pragmatic, cluster randomized clinical trial involving 2862 health care personnel, there was no significant difference in the incidence of laboratory-confirmed influenza among health care personnel with the use of N95 respirators (8.2%) vs medical masks (7.2%).

Meaning As worn by health care personnel in this trial, use of N95 respirators, compared with medical masks, in the outpatient setting resulted in no significant difference in the rates of laboratory-confirmed influenza.

Methods

Study Sites and Institutional Review Boards

The Respiratory Protection Effectiveness Clinical Trial (ResPECT) was approved by the human subjects research board at the National Institute for Occupational Safety and Health (protocol #10-NPPTL-05XP) and the institutional review boards (IRBs) at the 7 participating health systems, as previously described,[16] and approved or exempted by IRBs at the analysis and sample storage sites. All participants were permitted to participate for 1 or more years and gave written consent for each year of participation. Study intervention sites included outpatient settings at the Children's Hospital Colorado (Aurora), Denver Health Medical Center (Denver, Colorado), Johns Hopkins Health System (Baltimore, Maryland), Michael E. DeBakey Veterans Affairs (VA) Medical Center (Houston, Texas), VA Eastern Colorado Healthcare System (Denver), Washington DC VA Medical Center, and VA New York Harbor Healthcare System (New York). Sample storage and data analysis sites were the VA St Louis Healthcare System and St Louis University (St Louis, Missouri), University of Florida (Gainesville), University of Massachusetts (Amherst), and University of Texas Southwestern Medical Center (Dallas).

Design and Oversight

This cluster randomized, multicenter, pragmatic effectiveness trial[16] conducted between September 2011 and May 2015, with final follow-up on June 28, 2016, compared the effect of N95 respirators, used as recommended during the 2009 H1N1 pandemic,[13] and medical masks, used as recommended to prevent seasonal influenza[17,18] and other viral respiratory infections and illnesses, among HCP.[17] The investigators were blinded to the randomization until completion of the study and analysis. An independent data and safety monitoring board assessed the data. Additional details are included in Supplement 1, including the statistical analysis plan and the full protocol that was previously published in an abridged format.[16]

Participants and Setting

This trial was conducted in diverse outpatient settings serving adult and pediatric patients with a high prevalence of acute respiratory illness, including primary care facilities, dental clinics, adult and pediatric clinics, dialysis units, urgent care facilities and emergency departments, and emergency transport services.

All participants in a cluster worked in the same outpatient clinic or outpatient setting. A cluster randomized design was used to improve adherence and increase indirect effects associated with participants in a cluster using the same intervention. Participants were aged at least 18 years, employed at one of the 7 participating health systems, and self-identified as routinely positioned within 6 feet (1.83 m) of patients. Participants were full-time employees (defined as direct patient care for approximately ≥24 hours weekly) and worked primarily at the study site (defined as ≥75% of working hours). Exclusion criteria were medical conditions precluding safe participation or anatomic features that

Box 1. Criteria for Acute Respiratory Illness[a]

Signs
- Coryza
- Fever (temperature >37.8 °C)
- Lymphadenopathy
- Tachypnea (respiratory rate >25/min)

Symptoms
- Arthralgias/myalgias/body aches
- Chills
- Cough
- Diarrhea
- Dyspnea
- Fatigue
- Headache
- Malaise
- Other gastrointestinal systems
- Sore throat
- Sputum production
- Sweats
- Vomiting/nausea

[a] An acute respiratory illness was defined as the presence of at least 1 sign or 2 symptoms listed, representing a change from baseline.

could interfere with respirator fit, such as facial hair or third-trimester pregnancy. Participants self-identified race and sex using fixed categories; these variables were collected because facial anthropometrics related to race and sex may influence N95 respirator fit.

Participants kept diaries that included signs and symptoms of respiratory illness, annual influenza vaccination status, and exposure to household and community members with respiratory illness. Participants also recorded their participation in aerosol-generating procedures and exposure to patients, coworkers, or both with respiratory illness daily. Participants were categorized for exposure risk by occupational roles.

Procedures, Interventions, and Group Allocation

Each year, participating sites were cluster randomized to have participants wear N95 respirators[13] or medical masks,[17,18] as previously described.[16] N95 respirator models studied were the 3M Corporation 1860, 1860S, and 1870 (St Paul, Minnesota) and the Kimberly Clark Technol Fluidshield PFR95-270, PFR95-274 (Dallas, Texas); medical mask models were the Precept 15320 (Arden, North Carolina) and Kimberly Clark Technol Fluidshield 47107 (Dallas, Texas).

Within each medical center, for each study year, pairs of clusters (clinics and other settings) were matched by the number of participants, health services delivered, patient population served, and additional personal protective equipment. One cluster was randomly assigned to the medical mask group and one to the N95 respirator group. Random allocation of clusters required using constrained randomization, a process that maintains random assignment and balance between groups.[19] Computer-generated random sequences of group assignments were generated by an individual not involved in the study implementation and data analyses. Random sequences of assignment assured that every participant in each season had an equal probability of being assigned to the N95 respirator and medical mask groups and allowed participants to switch groups between seasons. Occupational Safety and Health Administration–accepted fit testing[15] of N95 respirators was conducted annually for all study participants.

Participants were instructed to wear their assigned protective devices (ie, N95 respirators or medical masks) during the 12-week period (the intervention period) during which the incidence of viral respiratory illness and infections was expected to be highest that year, as predicted by the ALERT algorithm[20] developed for this trial. Participants were instructed to put on a new device whenever they were positioned within 6 feet (1.83 m) of patients with suspected or confirmed respiratory illness. Hand hygiene was recommended to all participants in accordance with Centers for Disease Control and Prevention guidelines.[13,17,18] Infection prevention policies were followed at each study site. Participants volunteered to participate for up to 12 weeks each intervention period, for a total of 48 weeks of intervention spanning 4 consecutive viral respiratory seasons.

Surveillance, Outcomes, and Measures of Effectiveness

Study personnel obtained swabs of the anterior nares and oropharynx[21] (FLOQSwabs UTM, Diagnostic Hybrids) from participants who self-reported symptoms of respiratory illness (**Box 1**). Symptomatic swabs were collected within 24 hours of self-report, and again if signs or symptoms persisted beyond 7 days. If symptomatic participants were not at work, samples were self-obtained using a structured process and shipped to the study laboratory. During each 12-week intervention period, 2 random swabs were obtained from all participants, typically while asymptomatic. Additionally, each year, paired serum samples obtained from all participants were assayed for influenza hemagglutinin levels before and after peak viral respiratory season.

The prespecified primary outcome was the incidence of laboratory-confirmed influenza, defined as detection of influenza A or B virus by reverse-transcription polymerase chain reaction[22] in an upper respiratory specimen collected within 7 days of symptom onset; detection of influenza from a randomly obtained swab from an asymptomatic participant; or influenza seroconversion (symptomatic or asymptomatic), defined as at least a 4-fold rise in hemagglutination inhibition antibody titers to influenza A or B virus between preseason and postseason serological samples deemed not attributable to vaccination. Individuals experiencing seroconversion were not required to have a detected symptomatic illness to meet the defined outcome. Influenza reagents used in the hemagglutination inhibition antibody assays were obtained from the International Reagent Resource Program, established by the Centers for Disease Control and Prevention.

Secondary outcome measures were the incidence of 4 measures of viral respiratory illness and infection: (1) acute respiratory illness (Box 1) with or without laboratory confirmation; (2) laboratory-detected respiratory infection, defined as detection of a respiratory pathogen by polymerase chain reaction or serological evidence of infection with a respiratory pathogen during the study surveillance period(s), which was added to the protocol prior to data analysis; (3) laboratory-confirmed respiratory illness, identified as previously described,[23] defined as self-reported acute respiratory illness plus the presence of at least 1 polymerase chain reaction-confirmed viral pathogen (**Box 2**) in a specimen collected from the upper respiratory tract within 7 days of the reported symptoms and/or at least a 4-fold rise from preintervention to postintervention serum antibody titers to influenza A or B virus; and (4) influenzalike illness, defined as temperature of at least 100°F (37.8°C) plus cough and/or a sore throat, with or without laboratory confirmation.

Box 2. Respiratory Pathogens Assayed by Polymerase Chain Reaction

- Adenoviruses
- Coxsackie/echoviruses
- Coronavirus HKU1
- Coronavirus NL63
- Coronavirus OC43
- Coronavirus 229E
- Human metapneumovirus
- Human rhinovirus
- Influenza A
- Influenza B
- Parainfluenza virus type 1
- Parainfluenza virus type 2
- Parainfluenza virus type 3
- Parainfluenza virus type 4a
- Parainfluenza virus type 4b
- Respiratory syncytial virus type A
- Respiratory syncytial virus type B

Adherence to Group Assignment and Infection Prevention and Control Practices

Participants were reminded to adhere to protective device and hand hygiene instructions by signage posted at study sites, email, and by study personnel in person. Adherence to assigned devices were reported daily by participants as "always," "sometimes," "never," or "did not recall." In addition, study personnel observed participants' device-wearing behaviors as they entered and exited patient care rooms by conducting unannounced, inconspicuous visits to randomly selected study sites throughout the intervention period. However, to preserve patient confidentiality, monitors were not permitted to enter patient care rooms.

Statistical Analyses

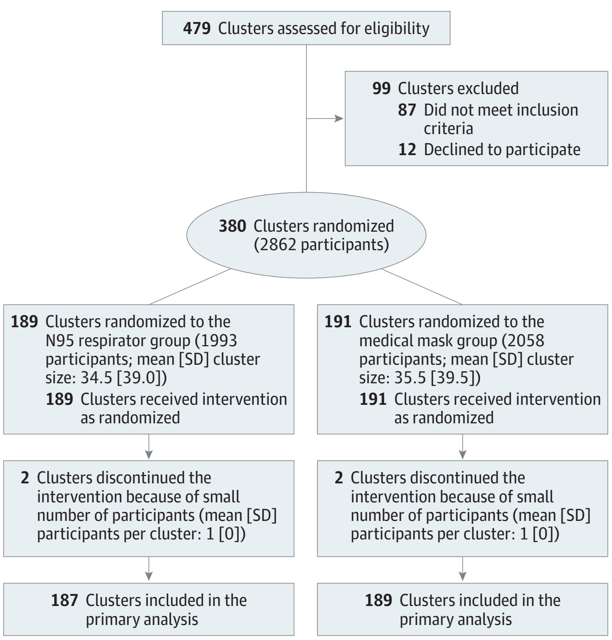
Although we identified no standard definition of a "clinically significant difference," this study[16] was designed to detect a 25% relative reduction in the incidence of laboratory-confirmed influenza or respiratory illness, based on expert opinion, rather than an absolute reduction, which has been described in a previous study.[6] The total sample size required to provide 80% power to show a 25% reduction in the incidence of laboratory-confirmed influenza in the N95 respirator group compared with the medical mask group, with a type I error rate of .05, was 10 024 participant-sessions, and the sample size needed to provide 80% power to show a 25% reduction in the incidence of laboratory-confirmed respiratory illness was 5104 participant-seasons.

Comparative effects of the interventions were estimated for the primary and secondary outcomes by calculating odds ratios (ORs; for binary outcomes) and incidence rate ratios (IRRs; for count outcomes) between participant clusters randomly assigned to wear N95 respirators or medical masks. Laboratory-confirmed influenza was modeled using logistic regression and viral respiratory infection and illness outcomes were modeled using Poisson regression. Unadjusted and adjusted analyses (both prespecified) were conducted according to the statistical analysis plan (Supplement 2). The primary outcome was an adjusted analysis, as specified in the statistical analysis plan. Prespecified covariates used in adjusted analyses included age, sex, race, number of household members younger than 5 years, occupation risk level (defined as low, medium, or high), binary season-specific influenza vaccination status, the proportion of daily exposures to others with respiratory illness, categorical self-reported adherence to hand hygiene, and intervention group assignment. Prespecified adherence rates were calculated as the proportion of reports of adherence in each group reporting "always," "sometimes," "never," or "did not recall." Comparison of proportions between groups were done using χ^2 statistics and comparisons of binomial proportions. Analyses included random effects to account for correlation of outcomes at site-level and individual-level random effects to account for correlation of outcomes at the individual level for participants who participated for multiple seasons.

The primary analysis used available data on all randomized participants for the primary comparison of the intervention. A per-protocol analysis, conducted at the same time as the primary analysis, included only individuals who completed at least 8 weeks of study participation.

A sensitivity analysis was conducted using imputation to assign outcomes to participants who did not complete the study. Missing outcomes were imputed using standard multiple imputation techniques, creating multiple imputed data sets with no missing values for each analysis.[23] Details of this analysis are described in Supplement 2. Intervention group withdrawal rates and time to withdrawal were compared to assess for potential bias. In an additional sensitivity analysis, observed and self-reported exposures and adherence were compared using Pearson χ^2 tests. Mean workplace and household rates of exposure to respiratory illness were compared using mixed-effects logistic regression. For

Figure 1. Study Site Enrollment, Randomization, Follow-up, and Analysis in a Study of the Effect of N95 Respirators vs Medical Masks for Preventing Laboratory-Confirmed Influenza Among Health Care Personnel



all calculations, a 2-sided type I error probability of .05 was used. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. All statistical analyses were performed in R version 3.3.3 (R Foundation).

Results

Participants

The study sites were randomized to provide 380 cluster-seasons of observation over 4 consecutive intervention periods. Of the 2862 participants, 1416 participated for more than 1 year or intervention period. Among 2862 unique randomized participants (mean [SD] age, 43 [11.5] years; 2369 [82.8%] women), 2371 completed the ResPECT protocol over the course of 48 weeks of intervention spanning 4 years. Among these individuals, 1446 participated in one 12-week intervention period, 723 participated in two 12-week intervention periods, and 693 participated in 3 or more 12-week intervention periods, accounting for 5180 HCP-seasons enrolled and randomized from 137 medical centers. Following randomization, 491 participants withdrew or were excluded because the cluster size was below a preestablished threshold of 2. Overall, 4689 HCP-seasons were included in the per-protocol analysis (2243 in the N95 respirator group and 2446 in the medical mask group; **Figure 1**). Some members of the primary analytic cohort did not complete all weeks of the study and were missing serological outcomes. Data were missing because of early withdrawal in 189 of 2512 participants (7.5%) in the N95 respirator group and 145 of 2668 (5.4%) in the medical mask group. In the per-protocol analysis, data were missing from 16 of 2243 participants (0.7%) in the N95 respirator group and 28 of 2446 (1.1%) in the medical mask group.

Baseline characteristics of the participants in the N95 respirator and medical mask groups were similar (**Table 1**). Daily workplace exposure to respiratory illness was reported 22.5% of the time in the N95 group and 21.6% of the time in the medical mask group, while weekly household exposure to respiratory illness was reported 3.6% of the time in the N95 respirator group and 3.4% of the time in the medical mask group (Table 1).

Illness Surveillance and Effectiveness

In the primary analysis, the incidence of laboratory-confirmed influenza infection events occurred in 207 of 2512 HCP-seasons (8.2%) in the N95 respirator group and 193 of 2668 HCP-seasons (7.2%) in the medical mask group, (difference, 1.0% [95% CI, −0.5% to 2.5%]; *P* = .18) (adjusted OR, 1.18 [95% CI, 0.95-1.45]).

Regarding secondary outcomes, there were 1556 acute respiratory illness events in the N95 respirator group (incidence rate [IR], 619.4 per 1000 HCP-seasons) vs 1711 in the medical mask group (IR, 641.3 per 1000 HCP-seasons) (difference, −21.9 per 1000 HCP-seasons [95% CI, −48.2 to 4.4]; *P* = .10; adjusted IRR, 0.99 [95% CI, 0.92-1.06]). There were 679 laboratory-detected respiratory infection events in the N95 respirator group (IR, 270.3 per 1000 HCP-seasons) vs 745 in the medical mask group (IR, 279.2 per 1000 HCP-seasons) (difference, −8.9 per 1000 HCP-seasons [95% CI, −33.3 to 15.4]; *P* = .47; adjusted IRR, 0.99 [95% CI, 0.89-1.09]) (**Table 2** and **Figure 2**). Overall, 371 laboratory-confirmed respiratory illness events occurred in the N95 respirator group (IR, 147.7 per 1000 HCP-seasons) vs 417 in the medical mask group (IR, 156.3 per 1000 HCP-seasons) (difference, −8.6 per 1000 HCP-seasons [95% CI, −28.2 to 10.9]; *P* = .39; adjusted IRR, 0.96 [95% CI, 0.83-1.11]). There were 128 influenzalike illness events in the N95 respirator group (IR, 51.0 per 1000 HCP-seasons) vs 166 in the medical mask group (IR, 62.2 per 1000 HCP-seasons) (difference, −11.3 per 1000 HCP-seasons [95% CI, −23.8 to 1.3]; *P* = .08; adjusted IRR, 0.86 [95% CI, 0.68-1.10]). Results were similar in the adjusted primary analysis and per-protocol analyses (Figure 2).

Intervention, Adherence, and Adverse Events

Adherence was reported on daily surveys 22 330 times in the N95 respirator group and 23 315 times in the medical mask group. “Always” was reported 14 566 (65.2%) times in the N95 respirator group and 15 186 (65.1%) times in the medical mask group; “sometimes,” 5407 (24.2%) times in the N95 respirator group and 5853 (25.1%) times in the medical mask group; “never,” 2272 (10.2%) times in the N95 respirator group and 2207 (9.5%) times in the medical mask group; and “did not recall,” 85 (0.4%) times in the N95 respirator group and 69 (0.3%) times in the medical mask group. Participant-reported adherence could not be assessed in 784 participants (31.2%) in the N95 respirator group and 822 (30.8%) in the medical mask group (*P* = .84)

Table 1. Health Care Personnel (HCP) Demographic Characteristics, Risk Factors, and Site Enrollment in a Study of the Effect of N95 Respirators vs Medical Masks for Preventing Laboratory-Confirmed Influenza

Characteristic	No. (%) N95 Respirator (n = 2512 HCP-Seasons)[a]	Medical Mask (n = 2668 HCP-Seasons)[a]
Age, mean (SD), y	43 (11.5)	43 (11.6)
Sex		
Men	378 (15.0)	420 (15.7)
Women	2134 (85.0)	2248 (84.3)
Ethnicity		
Hispanic or Latino	397 (15.8)	427 (16)
Race	(n = 2447)	(n = 2600)
White	1282 (52.4)	1334 (51.3)
Black	720 (29.4)	782 (30.1)
Other	232 (9.5)	252 (9.7)
Asian	195 (8.0)	210 (8.1)
American Indian or Alaska Native	14 (0.6)	13 (0.5)
Native Hawaiian or other Pacific Islander	4 (0.2)	9 (0.3)
Occupation		
Nurse/nursing trainee	1049 (41.8)	1085 (40.7)
Clinical care support staff[b]	574 (22.9)	627 (23.5)
Administrative/clerical	332 (13.2)	337 (12.6)
Other occupation	213 (8.5)	224 (8.4)
Physician/advanced practitioner/physician trainee	207 (8.2)	240 (9.0)
Registration/clerical reception	94 (3.7)	106 (4.0)
Social worker/pastoral care	35 (1.4)	29 (1.1)
Environmental services/housekeeping	8 (0.3)	19 (0.7)
Occupational risk[c]		
High	1492 (59.4)	1594 (59.7)
Medium	295 (11.7)	318 (11.9)
Low	724 (28.8)	755 (28.3)
Patient population		
Adult	1409 (56.1)	1486 (55.7)
Pediatric	573 (22.8)	557 (20.9)
Adult and pediatric	530 (21.1)	625 (23.4)
Clinic type		
Primary care	1734 (69.0)	1881 (70.5)
Emergent/urgent care	665 (26.5)	700 (26.2)
Emergency transport	42 (1.7)	33 (1.2)
Specialty care	40 (1.6)	29 (1.1)
Dental/dialysis	31 (1.2)	25 (0.9)
Site		
Johns Hopkins Health System	882 (35.1)	859 (32.2)
Denver Health	534 (21.3)	521 (19.5)
VA New York Harbor Healthcare System	375 (14.9)	433 (16.2)
The Michael E. DeBakey VA Medical Center	233 (9.3)	287 (10.8)
Washington DC VA Medical Center	183 (7.3)	204 (7.6)
VA Eastern Colorado Healthcare System	177 (7.0)	211 (7.9)
Children's Hospital Colorado	128 (5.1)	153 (5.7)

(continued)

Table 1. Health Care Personnel (HCP) Demographic Characteristics, Risk Factors, and Site Enrollment in a Study of the Effect of N95 Respirators vs Medical Masks for Preventing Laboratory-Confirmed Influenza (continued)

Characteristic	No. (%) N95 Respirator (n = 2512 HCP-Seasons)[a]	Medical Mask (n = 2668 HCP-Seasons)[a]
Comorbid conditions		
Asthma	255 (10.2)	284 (10.6)
Other systemic disease	104 (4.1)	118 (4.4)
Other respiratory disease	49 (2.0)	37 (1.4)
Cardiac disease	41 (1.6)	34 (1.3)
Chronic obstructive pulmonary disease	6 (0.2)	6 (0.2)
Influenza vaccination status	(n = 2444)	(n = 2598)
Vaccinated	1993 (79.3)	2048 (76.8)
Not vaccinated	451 (18.0)	550 (20.6)
Other risk factors		
Eyeglasses wearer	960 (38.2)	999 (37.4)
Household members aged <5 y	606 (24.1)	630 (23.6)
Contact lens wearer	371 (14.8)	349 (13.1)
Tobacco smoker	210 (8.4)	234 (8.8)
Exposure to respiratory illness, %		
Daily workplace	22.5	21.6
Weekly household	3.6	3.4

Abbreviation: VA, veterans affairs.

[a] Unless otherwise specified.

[b] Staff who have direct patient contact, such as clinical medical assistants and clinical technicians.

[c] Occupational risk based on direct patient contact, such as physical examination and/or performance of high-risk procedures (intubation, airway suctioning, nebulizer treatments, nasopharyngeal aspiration) for high risk, direct patient contact for medium risk, and no or minimal direct patient contact for low risk.

because of lack of response to surveys or lack of adherence opportunities (ie, participants did not encounter an individual with respiratory signs or symptoms).

Analyzed post hoc, participant adherence was reported as always or sometimes 89.4% of the time in the N95 respirator group and 90.2% of the time in the medical mask group. Additional details about adherence are included in Supplement 1. No serious study-related adverse events were reported. Nineteen participants reported skin irritation or worsening acne during years 3 and 4 at one study site in the N95 respirator group.

Per-Protocol Analysis and Sensitivity Analysis

Results of the per-protocol analysis can be seen in Figure 2. A sensitivity analysis assessed whether there was evidence for bias in self-reported outcomes based on group assignment. In a prespecified multiple-imputation analysis, the rates of laboratory-confirmed influenza infection events were 204 of 2243 HCP seasons (9.1%) in the N95 respirator group and 190 of 2446 HCP-seasons (7.8%) in the medical mask group. Quantitative data are available in Supplement 3.

Table 2. Primary and Secondary Outcomes in a Study of the Effect of N95 Respirators vs Medical Masks for Preventing Laboratory-Confirmed Influenza Among Health Care Personnel

Primary and Secondary Outcome Events	No.									
	2011-2012		2012-2013		2013-2014		2014-2015		Totals	
	N95 Respirator	Medical Mask	N95 Respirator	Medical Mask	N95 Respirator	Medical Mask	N95 Respirator	Medical Mask	N95 Respirator	Medical Mask
Influenza (primary outcome)										
Polymerase chain reaction-detected										
Influenza A	2	3	19	19	8	12	37	28	66	62
Influenza B	0	3	8	11	2	1	1	4	11	19
Hemagglutination inhibition assay-detected										
Influenza A	5	9	30	23	38	38	55	47	128	117
Influenza B	0	2	10	11	12	13	14	10	36	36
All events[a]										
Influenza A	6	10	43	37	46	42	85	65	180	154
Influenza B	0	5	15	18	12	14	15	13	42	50
All influenza	6	15	58	55	58	56	100	78	222	204
Laboratory-confirmed influenza	6	13	52	52	55	51	94	77	207	193
Secondary Outcomes										
Acute respiratory illness	235	234	354	446	398	519	569	512	1556	1711
Laboratory-detected respiratory infection[b]	47	71	165	201	217	260	250	213	679	745
Laboratory-confirmed respiratory illness[b]	26	31	91	116	111	150	143	120	371	417
Influenzalike illness	13	10	30	45	22	50	63	61	128	166

[a] Influenza events were defined as the number of influenza infections attributed to the combination of polymerase chain reaction detection and hemagglutination inhibition assay serologies. Instances in which polymerase chain reaction and hemagglutination inhibition assay were both positive counted as 1 event.

[b] All respiratory viruses assayed, including influenza.

Discussion

In this pragmatic, cluster randomized trial that involved multiple outpatient sites at 7 health care delivery systems across a wide geographic area over 4 seasons of peak viral respiratory illness, there was no significant difference between the effectiveness of N95 respirators and medical masks in preventing laboratory-confirmed influenza among participants routinely exposed to respiratory illnesses in the workplace. In addition, there were no significant differences between N95 respirators and medical masks in the rates of acute respiratory illness, laboratory-detected respiratory infections, laboratory-confirmed respiratory illness, and influenzalike illness among participants. A sensitivity analysis suggested that the primary analysis reported was fairly robust to the missing outcome data with quantitative outcomes varying by less than 5%. This supports the finding that neither N95 respirators nor medical masks were more effective in preventing laboratory-confirmed influenza or other viral respiratory infection or illness among participants when worn in a fashion consistent with current US clinical practice.

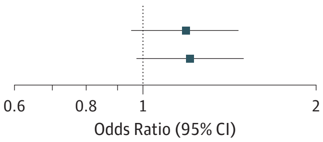
Respiratory viruses are primarily transmitted by large droplets. Because a fraction of respiratory viruses may be transmitted by aerosol, N95 respirators have been presumed to provide better protection than medical masks against viral respiratory infections in health care settings.[2] However, definitive evidence of greater clinical effectiveness of N95 respirators is lacking. A well-designed trial[6] found the effectiveness of medical masks to be noninferior to N95 respirators, but the trial was stopped prematurely and was limited by small sample size. Two additional studies[3,4] (and a pooled analysis[12]) concluded that N95 respirators may be more effective than medical masks; however, these studies were limited by uncertain clinical significance of end points.[24] The current study was undertaken because of remaining uncertainty based on previous studies, which made it challenging for infection control clinicians to effectively implement respiratory protection programs in health care settings.[2,7,13,18,24,25]

This trial was designed to assess clinical effectiveness, taking into account many challenges of working in outpatient health care settings. This study had several strengths, including the pragmatic design; wide US geographic and climatic distribution; varied adult and pediatric outpatient settings, including emergency departments; and enrollment spanning 4 seasons of peak viral respiratory illness. Respiratory samples were obtained from symptomatic and asymptomatic participants to determine the incidence of viral respiratory infection, including individuals that were subclinical but still potentially transmissible. Influenza vaccination status information was collected. This trial was cluster randomized to avoid mixing of interventions in each clinic and clinical setting and to minimize cross-contamination from

Figure 2. Primary and Secondary Outcomes of Influenza and Respiratory Illnesses and Adjusted Risk Estimates Among Health Care Personnel in the N95 Respirator Group vs the Medical Mask Group

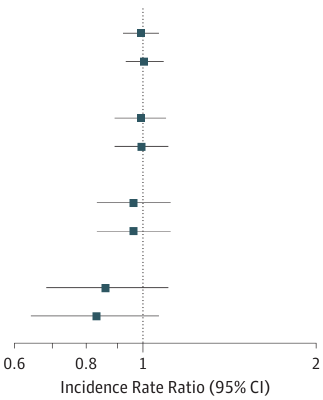
A Primary outcome

	N95 Respirator Events/Seasons	Medical Mask Events/Seasons	Incidence Rate Ratio (95% CI)
Laboratory-confirmed influenza			
ITT cohort	207/2512	193/2668	1.18 (0.95-1.45)
PP cohort	204/2243	190/2446	1.20 (0.97-1.48)



B All secondary outcomes

	N95 Respirator Events/Seasons	Medical Mask Events/Seasons	Incidence Rate Ratio (95% CI)
Acute respiratory illness			
ITT cohort	1556/2512	1711/2668	0.99 (0.92-1.06)
PP cohort	1512/2243	1656/2446	1.00 (0.93-1.08)
Laboratory-detected respiratory infection			
ITT cohort	679/2512	745/2668	0.99 (0.89-1.09)
PP cohort	664/2243	733/2446	0.99 (0.89-1.10)
Laboratory-confirmed respiratory illness			
ITT cohort	371/2512	417/2668	0.96 (0.83-1.11)
PP cohort	361/2243	406/2446	0.96 (0.83-1.11)
Influenzalike illness			
ITT cohort	128/2512	166/2668	0.86 (0.68-1.10)
PP cohort	121/2243	161/2446	0.83 (0.64-1.06)



The adjusted relative risks for the N95 respirator and medical mask groups for both the intention-to-treat (ITT) and per-protocol (PP) groups for the primary outcome and the other predetermined secondary outcomes. Values above 1 indicate higher relative odds or risk in the N95 respirator group compared with the medical mask group.

different HCP behaviors, conducted at 7 medical centers among frontline HCP in varied clinical settings with high exposure risk, and sufficiently powered to detect the predefined difference in laboratory-confirmed respiratory illness. Previous effectiveness studies[3,4,6,12,26-28] have met some, but not all, of these characteristics and have been inconclusive, contributing to the uncertainty and controversy among experts determining public health guidance, regulatory requirements, and health care delivery practices.[2,7,14,17,29] In the current study, findings were consistent across all laboratory-based outcomes and clinical syndromes. Results for the primary and secondary outcomes were in opposite directions (ie, one IRR was associated with increased risk and the other with decreased risk), although the differences were nonsignificant, further supporting a finding of no significant difference in the effectiveness of N95 respirators vs medical masks for prevention of influenza or other respiratory illness.

Limitations

This study has several limitations. First, the criteria for viral polymerase chain reaction testing may have missed participants who were infected but asymptomatic. Unrecognized infections may have increased the probability of finding no difference between interventions, even if a difference existed. Second, self-reporting of symptoms in daily diaries likely underestimated illness among HCP who often work while ill.[30] Third, despite being intentionally conducted as a pragmatic effectiveness trial,[8] incomplete participant adherence to assigned protective devices could have contributed to more unprotected exposures, increasing the probability of finding no difference between interventions even if a difference existed. However, participant-reported data indicates this did not differ by study group. Fourth, participants were not instructed to wear protective devices outside the workplace, which may have biased the results toward finding no difference between groups, although the rates of adherence did not differ by study group and household exposure was reported as much lower than workplace exposure. Fifth, only 2 N95 respirator and medical mask models were studied, limiting the ability to generalize about the protectiveness of other models. Sixth, the sample size required to definitively determine whether N95 respirators or medical masks are more effective for protection from laboratory-confirmed influenza in the health care setting required approximately 10 000 participant-seasons, which was not feasible with the available funding or resources. However, the morbidity and mortality associated with a wide range of viral respiratory infections, including novel and emerging pathogens, renders a secondary outcome in this study, laboratory-confirmed respiratory illness, important.

Conclusions

Among outpatient HCP, N95 respirators vs medical masks as worn by participants in this trial resulted in no significant difference in the incidence of laboratory-confirmed influenza.

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