A Randomized Clinical Trial of Three Options for N95 Respirators and Medical Masks in Health Workers

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Rationale: **We compared three policy options for the use of medical masks and N95 respirators in healthcare workers (HCWs).**
Objectives: **A cluster randomized clinical trial of 1,669 hospital-based HCWs in Beijing, China in the winter of 2009–2010.**
Methods: **Participants were randomized to medical masks, N95 respirators, or targeted use of N95 respirators while doing high-risk procedures or barrier nursing. Outcomes included clinical respiratory illness (CRI) and laboratory-confirmed respiratory pathogens in symptomatic subjects.**
Measurements and Main Results: **The rate of CRI was highest in the medical mask arm (98 of 572; 17%), followed by the targeted N95 arm (61 of 516; 11.8%), and the N95 arm (42 of 581; 7.2%) ($P < 0.05$). Bacterial respiratory tract colonization in subjects with CRI was highest in the medical mask arm (14.7%; 84 of 572), followed by the targeted N95 arm (10.1%; 52 of 516), and lowest in the N95 arm (6.2%; 36 of 581) ($P = 0.02$). After adjusting for confounders, only continuous use of N95 remained significant against CRI and bacterial colonization, and for just CRI compared with targeted N95 use. Targeted N95 use was not superior to medical masks.**
Conclusions: **Continuous use of N95 respirators was more efficacious against CRI than intermittent use of N95 or medical masks. Most policies for HCWs recommend use of medical masks alone or targeted N95 respirator use. Continuous use of N95s resulted in significantly lower rates of bacterial colonization, a novel finding that points to more research on the clinical significance of bacterial infection in symptomatic HCWs. This study provides further data to inform occupational policy options for HCWs.**
Clinical trial registered with Australian New Zealand Clinical Trials Registry http://www.anzctr.org.au (ACTRN 12609000778280).

Keywords: randomized clinical trial; N95 respirator; medical mask; healthcare workers

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The use of respiratory protection in health workers is impacted by entrenched practices that have not had an adequate evidence base to support them. Most policies for healthcare workers recommend use of medical masks alone or targeted N95 respirator use.

What This Study Adds to the Field

We tested policy recommendations in a randomized controlled trial and found that continuous use of N95s resulted in significantly lower rates of clinical respiratory infection compared with targeted use in high-risk situations, or use of medical masks. These new data inform occupational policy options for healthcare workers and have significance for occupational health and safety.

INTRODUCTION

The risks of influenza pandemics (1), emerging infections, and antimicrobial resistance are safety concerns for healthcare workers (HCWs). The role of respiratory protection for HCWs has been debated in recent years. N95 filtering face-piece respirators (from here on referred to as "N95 respirators") are designed for respiratory protection and defined by their filtration capacity (2), which is higher than that of medical masks (3–5). The original purpose of medical masks was to prevent microbial contamination of wounds while worn by surgeons during surgery (hence their common name "surgical masks"), yet randomized controlled trials show no efficacy against wound contamination (6–8).

Masks in community settings have no clearly proved efficacy (9–14). In three trials, participants were randomized either to hand washing or to hand washing plus surgical masks (9, 11, 13), with no clear additional benefit of masks. We have previously shown that masks in compliant users in the household setting reduced the risk of influenza-like illness (ILI) (12). There have also been two randomized controlled trials of medical masks compared with N95 respirators in HCWs (15, 16). The first found no difference between the arms, but was a small study, lacked a control arm, and was based predominantly on serologic diagnosis of influenza (15). We previously found that all infection outcomes were consistently lower for the N95 arm compared with medical masks, and that N95 respirators were significantly more protective than medical masks against clinical respiratory infection (16).

Previous work has focused on the use of respiratory protection to prevent clinical respiratory illness (CRI) and viral infections, such as influenza (15, 16). Respiratory tract colonization by bacterial pathogens has never been studied in this context, despite the common practice of using masks when in contact with patients with bacterial infections, such as tuberculosis.

The aim of this study was to determine the efficacy of three different options for the use of masks and respirators in HCWs working in high-risk hospital wards, in the prevention of respiratory infections.

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METHODS

We conducted a cluster randomized trial of three policy options for the use of medical masks and respirators in HCWs from December 28, 2009 to February 7, 2010 (the winter season) in Beijing, China. Participants were randomized by ward to three arms: (*1*) medical masks at all times on shift; (*2*) N95 respirators at all times on shift; and (*3*) targeted (intermittent) use of N95 respirators only while doing high-risk procedures or barrier. The targeted N95 arm was studied because policies in many countries advocate the use of N95 respirators only when the HCW is in a high-risk situation, such as barrier nursing of a patient with known respiratory illness or when conducting aerosol-generating procedures. HCWs were given a checklist of defined high-risk procedures, which included common aerosol-generating procedures. The continuous N95 arm was incorporated to measure any dose–response effect of continuous compared with targeted N95 use; this option also reflects current practice in high-risk settings in China.

The study protocol was approved by the Institutional Review Board and Human Research Ethics Committee of the Beijing Center for Disease Prevention and Control and from the Human Research Ethics Committee of University of New South Wales, Australia. Written informed consent was provided by participants before the study. There were no incentives used.

Randomization

Sixty-eight emergency departments and respiratory wards of 19 tertiary hospitals in Beijing were selected as high-risk settings for occupational risk of exposure to respiratory infections. Randomization was done after eligibility assessment as shown in Figure 1, in the first week of December 2009. Cluster randomization was selected as the most appropriate method for two reasons. First, HCWs in China found it more acceptable to participate if the same intervention was offered to all their colleagues in the ward. Second, the outcome of interest is respiratory infectious diseases known to be transmitted person-to-person, so that preventing infection through mask use in one HCW may reduce the risk of infection in other HCWs in hospital wards and other closed settings. More detail has been published in our previous work (12, 16).

Eligibility

Any nurse or doctor aged 18 years or older who worked full-time in the emergency or respiratory wards was eligible. HCWs were excluded if they (*1*) were unable or refused to consent; (*2*) had beards, long moustaches, or long facial hair stubble; (*3*) had a current respiratory illness, rhinitis, and/or allergy; or (*4*) worked part-time or did not work in the aforementioned wards or departments.

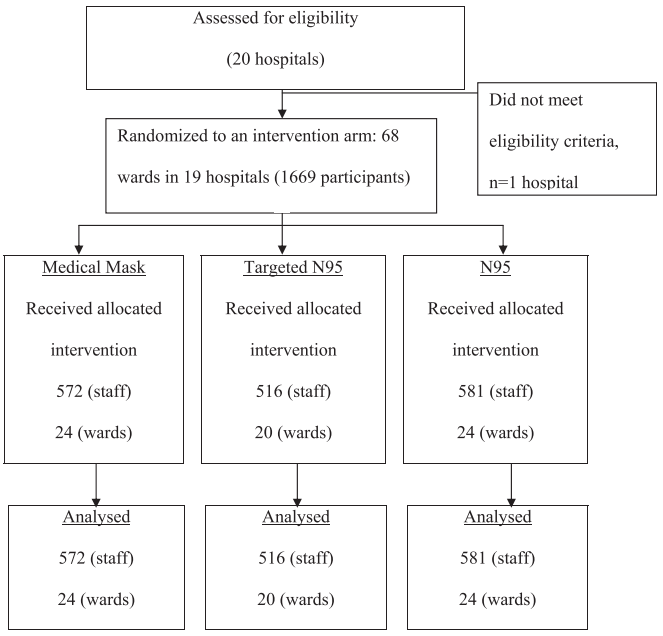

Figure 1. Consort diagram of recruitment and follow-up.

Intervention

Masks used in the study were the 3M Standard Tie-On Surgical Mask (catalog number mask 1817; 3M, St. Paul, MN) and the 3M Health Care N95 Particulate Respirator (catalog number 1860; 3M). Figure 1 outlines the recruitment and randomization (using a secure computerized randomization program) process. Participants wore the mask or respirator on every shift after being shown how to fit and wear it. Participants were supplied daily with either three masks for the medical mask arm or two N95 respirators. Participants using N95 respirators underwent a fit testing procedure using a 3M FT-30 Bitrex Fit Test Kit according to the manufacturer's instructions (3M). Subjects who failed the fit test participated in the trial by intention to treat, using the N95 respirator.

Primary Endpoints

The primary endpoints included the following:

1. CRI, defined as two or more respiratory symptoms or one respiratory symptom and a systemic symptom (16, 17).
2. ILI, defined as fever (38°C) plus one respiratory symptom.
3. Laboratory-confirmed viral respiratory infection in symptomatic subjects, defined as detection of adenoviruses; human metapneumovirus; coronaviruses 229E/NL63 and OC43/HKU1; parainfluenza viruses 1, 2, and 3; influenza viruses A and B; respiratory syncytial viruses A and B; or rhinoviruses A/B by nucleic acid testing (NAT) using a commercial multiplex polymerase chain reaction (Seegen, Inc., Seoul, Korea).
4. Laboratory-confirmed influenza A or B in symptomatic subjects.
5. Laboratory-confirmed bacterial colonization in symptomatic subjects, defined as detection of *Streptococcus pneumoniae*, legionella, *Bordetella pertussis*, chlamydia, *Mycoplasma pneumoniae*, or *Haemophilus influenzae* type B by multiplex polymerase chain reaction (Seegen, Inc.).

Cost precluded testing all subjects, so asymptomatic subjects were not tested. Anyone with a single respiratory symptom or fever was tested for outcomes 3–5 listed previously. This was chosen as a highly sensitive trigger for testing, and includes symptomatic subjects who did not meet the CRI definition.

The choice of a broad CRI definition, also used in our previous studies (12, 16), was dictated by our interest in interrupting transmission of a wide range of respiratory pathogens, many of which may not present with fever in adults. Additional endpoints included adherence with mask or respirator use (defined as using the mask or respirator during the shift for 70% or more of shift hours) and adverse effects, measured using a semistructured questionnaire (16).

Data Collection and Follow-Up

Data on demographics and potential confounders were collected at baseline, including age, sex, smoking status, comorbidities, and prior influenza vaccination. Participants were followed for 4 weeks of wearing the masks or respirators, and an extra week of nonwearing of masks for development of symptoms during the incubation period of infections acquired in Week 4. Participants received a thermometer and diary cards for the study duration to record daily the number of hours worked, mask or respirator use, number of high-risk procedures undertaken, and development of symptoms. Participants were contacted daily to identify incident cases of respiratory infection. If participants were symptomatic, swabs of both tonsils and the posterior pharyngeal wall were collected on the day of reporting. We also monitored adherence with mask or respirator use by a previously validated self-reporting mechanism (16). Briefly, the self-report instrument was a pocket-sized diary card with tick boxes for mask use, which was carried by staff during the day and filled in daily and collected at the end of each day by study staff.

Sample Collection and Laboratory Testing

Double rayon-tipped, plastic-shafted swabs were used to scratch both tonsilar areas and the posterior pharyngeal wall of symptomatic subjects. These were then transported immediately after collection to the Beijing Center for Disease Control laboratories, or stored at 4°C up to 48 hours if transport was delayed. The method for the NAT of swabs has been previously described (16) and is available in the online supplement.

Analysis

Primary endpoints were analyzed by intention to treat. Laboratory outcomes are reported for all subjects (with at least one respiratory symptom or fever) tested, and then for the subset meeting the CRI definition. We compared the event rates for the primary outcomes across study arms and calculated a *P* value from cluster-adjusted chi-square tests (18) and intracluster correlation coefficients (ICC) (18, 19). Using time to event, Kaplan-Meier survival curves with and without adjusting for clustering and other potential confounders were used to compare the survival pattern of outcomes across the three arms. Log-rank test and log-rank test for trend were also conducted to assess the difference among the survival curves (20). We estimated the effect measure as hazard ratios (HR). A multivariable Cox proportional hazards model was used to estimate HR after adjusting for potential confounders that were unequally distributed between the study arms. To adjust for the clustering effect we used cluster-correlated robust estimate of variance method to estimate the standard error of the HR (21). As a sensitivity analysis we also estimated the HR only including the compliant subjects (per protocol analysis). All statistical analyses were conducted using STATA version 12 (2011, Stata Statistical Software: Release 12; StataCorp, College Station, TX).

Sample Size Calculation

To obtain 80% power at two-sided 5% significant level for detecting a significant difference of attack rate between the intervention arms, and for an assumed 3.9% CRI attack rate in the N95 arm and 9.2% in the medical mask arm, a sample size of 558 participants or 23 clusters (wards) per arm was required for cluster size (m) 25 and ICC 0.027, obtained from our previous study (18). The design effect (deff) for this cluster randomization trial was 1.65 (deff = 1 + [m − 1] × ICC = 1 + [25 − 1] × 0.027 = 1.65). As such, we aimed to recruit a sample size of 560 (23 clusters) per arm (18).

RESULTS

A total of 1,669 nurses and doctors in 68 wards from 19 Beijing hospitals were recruited into the study, and 100% of eligible health workers participated. The average cluster size (number of participants per ward) was 24.5. The distribution of demographic variables was generally similar between arms (Table 1), but was significantly different for age, A(H1N1)pdm09 influenza vaccination in 2010, seasonal influenza vaccination in 2009, self-reported hand washing, and staff type (doctor or nurse). The fit test failure rate in the N95 arms was very low, at 2.6% (28 of 1,086).

Table 2 shows the intention-to-treat analysis. The rate of CRI was highest in the medical mask arm (98 of 572; 17%); followed by the targeted N95 arm (61 of 516; 11.8%); and lowest in the N95 arm (42 of 581; 7.2%) ($P < 0.05$). There were six laboratory-confirmed cases of influenza: four A(H1N1)pdm09 and two influenza B. Other respiratory viruses were identified in 43 subjects, the most frequent being respiratory syncytial virus (n = 17). Rates of laboratory-confirmed respiratory virus infections were low and not significant between arms: the medical mask arm (19 of 572; 3.3%); targeted N95 arm (17 of 516; 3.3%); and N95 arm (13 of 581; 2.2%) ($P = 0.44$). Table 2 shows that the rates of detection of bacterial pathogens in subjects with CRI were highest in the medical mask arm (84 of 572; 14.7%); followed by the targeted N95 arm (52 of 516; 10.1%); and lowest in the N95 arm (36 of 581; 6.2%) ($P = 0.02$). The same trend was seen in subjects with any symptom, as shown in Table 2. Among all subjects tested (those with at least one symptom) the most common bacteria identified was *S. pneumoniae*, with 110 of 572 (19%) in the medical mask arm; 68 of 516 (13%) in the targeted arm; and 46 of 581 (8%) in the N95 arm ($P < 0.001$). The next most frequent bacteria identified was *H. influenzae* type B; then *B. pertussis* (n = 1); *Chlamydia pneumonia* (n = 2); and *M. pneumoniae* (n = 3). Bacterial coinfection was common, as shown in Table 3, with a statistically significant trend to increasing coinfection with two of more bacteria with decreasing respiratory protection. The most common coinfection was *S. pneumoniae* and *H. influenza* B (n = 128 across all three arms). Dual virus coinfections occurred in 19 subjects and coinfection with a virus and bacteria in 42 subjects (Table 3).

Kaplan-Meier curves (Figure 2) showed a significant advantage of N95 masks alone over the targeted N95 arm, which in turn was better than medical masks alone, for CRI and bacterial colonization in subjects with CRI. The log-rank test and

TABLE 1. DEMOGRAPHIC AND OTHER CHARACTERISTICS OF PARTICIPANTS BY RANDOMIZATION ARM

Variable	Medical Mask (*n = 572*)	Targeted N95 (*n = 516*)	N95 (*n = 581*)	*P* Value*
Sex, male	92/572	68/516	83/581	0.390
	16.1%	13.2%	14.3%	
Age, mean (SD)	34.20 (10.3)	31.34 (8.4)	33.59 (9.7)	**<0.0001**†
University education	271/572	211/516	242/581	0.057
	47.4%	40.9%	41.7%	
Current smoker	23/572	16/516	24/581	0.624
	4.0%	3.1%	4.1%	
Household size ⩾4	99/572	102/516	118/581	0.389
	17.3%	19.8%	20.3%	
A(H1N1)pdm09 vaccination 2009–2010	109/572	130/516	171/581	**<0.001**
	19.1%	25.2%	29.4%	
Seasonal influenza vaccination 2009–2010	88/572	51/516	85/581	**0.017**
	15.4%	9.9%	14.6%	
Staff, doctors	235/572	162/516	214/581	**0.004**
	41.1%	31.4%	36.8%	
Reported hand washing after patient contact at all times	417/572	313/516	448/581	**0.0001**
	72.9%	60.7%	77.1%	
Ill household contact during trial	10/572	8/513	10/576	0.965
	1.75%	1.56%	1.74%	
Undertook high-risk procedure	408/571	398/516	417/581	0.062
	71.5%	77.1%	71.8%	

Bold indicates significant *P* values ($P < 0.05$).

* Pearson chi-square test for comparison of proportions across three arms, unless otherwise indicated.

† One-way analysis of variance.

TABLE 2. NUMBER AND PROPORTION OF PARTICIPANTS REPORTING PRIMARY OUTCOMES, BY RANDOMIZATION ARM AND INTENTION-TO-TREAT ANALYSIS

Variable	Medical Mask Arm N (%)	Targeted N95 Arm		N95 Arm	
		N (%)	*P* Value (ICC)*	N (%)	*P* Value (ICC)†
CRI	98/572 (17.1)	61/516 (11.8)	0.280 (0.1166)	42/581 (7.2)	**0.0238** (0.1194)
ILI	4/572 (0.7)	2/516 (0.4)	0.4882 (<0.0001)	6/581 (1.0)	0.5416 (<0.001)
Virus	19/572 (3.3)	17/516 (3.3)	0.985 (0.0206)	13/581 (2.2)	0.4394 (0.0311)
Bacteria + CRI	84/572 (14.7)	52/516 (10.1)	0.27 (0.091)	36/581 (6.2)	**0.019** (0.086)
Bacteria (any symptoms)‡	120/572 (21.0)	75/516 (14.5)	0.2448 (0.1279)	52/581 (9.0)	**0.0163** (0.1338)
Virus or bacteria + CRI	91/572 (15.9)	56/516 (10.8)	0.260 (0.100)	39/581 (6.7)	**0.022** (0.102)
Virus or bacteria (any symptoms)	123/572 (21.5)	77/516 (14.9)	0.2484 (0.1339)	52/581 (9.0)	**0.016** (0.1442)
Influenza A or B + CRI	1/572 (0.2)	2/516 (0.4)	0.5898 (0.145)	3/581 (0.5)	0.3241 (<0.001)

Definition of abbreviations: CRI = clinical respiratory illness; ICC = intracluster correlation coefficient; ILI = influenza-like illness.
Bold indicates significant *P* values ($P < 0.05$).
* Cluster adjusted *P* value from chi-square test comparing targeted N95 with medical mask arm and the ICC.
† Cluster adjusted *P* value from chi-square test comparing N95 with medical mask arm and the ICC.
‡ Threshold for testing was one symptom.

log-rank test for trend (results not shown in a table) for all outcomes were highly significant ($P < 0.001$). The HR ratio for CRI and bacterial colonization after adjusting for clustering effect and other potential confounders are given in Table 4 using the medical mask arm as the referent group, and shows that N95 but not targeted N95 remains significantly protective against CRI and bacterial colonization. The only other significant variable was seasonal influenza vaccination, which was protective against CRI only, but not against bacterial colonization. Using targeted N95 as the referent group, N95 was significantly protective against CRI (HR, 0.56; 95% confidence interval, 0.32–0.98) but not for bacterial colonization (results not tabulated). There was no difference for ILI or laboratory-confirmed viral infections. The per protocol analysis of compliant participants showed essentially the same result, but with the protective effect of N95 increasing compared with Table 4 (HR for N95, 0.35 [0.17–0.73] for CRI; HR, 0.37 [0.17–0.79] for bacterial colonization).

Compliance with the product was the highest in the targeted N95 arm (82%; 422 of 516), then the medical mask arm (66%; 380 of 572), and the N95 arm (57%; 333 of 581) and these differences were statistically significant ($P < 0.001$). In terms of comfort, 52% (297 of 571) of the medical mask arm reported no problems, compared with 62% (317 of 512) of the targeted arm and 38% (217 of 574) of the N95 arm ($P < 0.001$).

DISCUSSION

In a setting of high occupational risk for HCWs, the key observation of this study is significant protective efficacy against clinical infection of continuous use of N95 respirators compared with targeted use and medical masks, despite significantly poorer adherence in the continuous use N95 arm. These results add weight to the findings of our previous study (16) that showed that N95 respirators have superior clinical efficacy to medical masks, despite the greater discomfort and lower adherence associated with respirator use. We also showed that the benefit of N95 respirators persisted after adjusting for the potential confounding by influenza vaccination and hand washing. The trade-off posed by proved efficacy in settings where mask wearing is not as widely accepted as in China needs to be considered in different cultural contexts. However, we were unable to show a difference between the targeted N95 arm and medical mask arm, both reflecting common practice in developed countries, which could indicate equal inefficacy or equal efficacy of a magnitude too small to detect in this trial. Without a control arm (i.e., no masks), which is ethically difficult to undertake in hospital HCWs in China, this question cannot be resolved, but our previous trial showed no superiority of medical masks against control subjects (16). This current study has significant occupational health and safety implications for HCWs if potentially ineffective policy options are recommended.

The study by Loeb and coworkers (15) that has widely informed policy decisions found no difference between N95 respirators and medical masks, but was probably underpowered, with only 446 subjects in the trial. Power is an issue in that study because the serologic endpoints used to define "influenza" may include a high proportion of false-positives (see below). Indeed, the rate of "influenza" found in that study (~24%) is the same as rates of influenza documented in nosocomial outbreaks of influenza in HCWs without preventive interventions (22), and actually higher than rates described in other studies of influenza in unprotected HCWs (23), suggesting that the endpoint overestimated influenza and that both interventions had equal inefficacy. Importantly, the intervention studied in the Loeb trial was the use of medical masks and respirators only during care of identified febrile patients with ILI or having high-risk procedures, and where the unit of randomization was blocks of four HCW (15). Our study included a similarly targeted use of N95 respirators when HCWs were conducting high-risk procedures or entering an isolation room, but compared this with the wearing of N95 respiratory protection for the entire shift. The policy of targeted use of N95 respirators requires the HCW to identify each clinical contact that is high-risk, and then don the respirator. Whether targeted use of masks or respirators is protective depends on whether HCWs can accurately identify all episodes of risk, whether transmission occurs only during clearly identified exposures, and whether there is transmission from asymptomatic or presymptomatic individuals. There is currently little evidence on how much of a HCW's occupational risk of respiratory infection is unidentified or unrecognized. Previously, we found that HCWs who conducted high-risk procedures had higher rates of CRI (16). This study may further assist in making policy not just for the type of respiratory protection needed for HCWs in situations of high risk, but continuous versus targeted mask use.

We used a broad definition of CRI to allow the inclusion of the full spectrum of clinical syndromes associated with respiratory

TABLE 3. COINFECTION WITH MULTIPLE BACTERIA OR BACTERIA/VIRUS

Coinfection	N95	Targeted	Medical	*P* Value
≥2 bacteria	5.2% (30/581)	7.8% (40/516)	11.2% (64/572)	**<0.001**
≥2 viruses	1.0% (6/581)	1.0% (5/516)	1.4% (8/572)	0.766
Virus and bacteria	2.2% (13/581)	2.9% (15/516)	2.5% (14/572)	0.773

Bold indicates significant *P* values ($P < 0.05$).

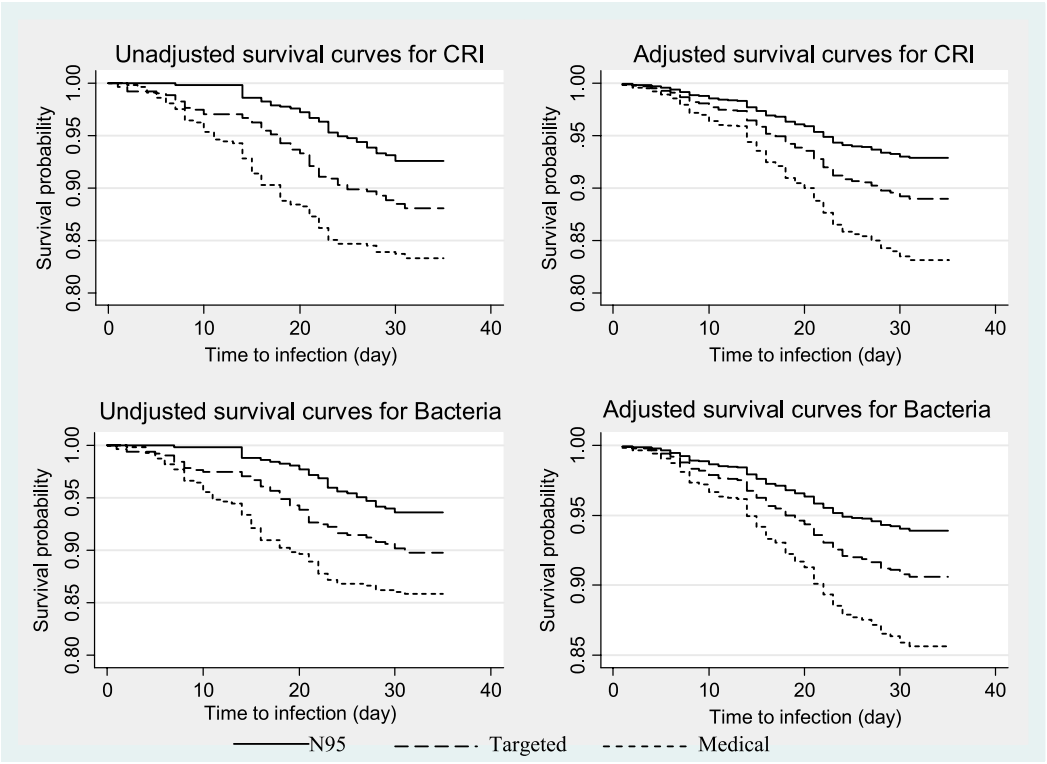

Figure 2. Adjusted and unadjusted Kaplan-Meier survival curves for CRI and bacteria detection for the three intervention arms. Adjusted for all variables included in the multivariate Cox model and clustering (Table 3). CRI = clinical respiratory illness.

infections in adults, including respiratory infection in the absence of fever. We showed that this definition was justified, with only (12%) of subjects with a laboratory-confirmed respiratory virus having fever as an accompanying symptom. Our study confirms that adults do not commonly have fever with viral respiratory tract infections. Furthermore, we tested any subject who was symptomatic, even if they did not meet the CRI definition. The high rate of detection of bacteria in symptomatic HCWs was a surprising finding, and may represent colonization rather than infection. A comparison of rates of bacterial detection in symptomatic and asymptomatic HCWs (and whether the process of potentially pathogenic bacterial colonization in itself may be associated with mild symptomatology) is needed to address this question. Such studies are currently unavailable.

Bacterial colonization is less well studied in HCWs, but there is emerging evidence that questions the long-held view that bacterial colonization is meaningless. Bacterial carriage density may be a predictor of invasive disease and of viral-bacterial coinfection (24). There is also an increased susceptibility of the respiratory tract to viral infection after bacterial infections and *vice versa*, most well described around the relationship between influenza and pneumococcus (25–28). Bacterial coinfections commonly occur during influenza outbreaks (29). *S. pneumoniae*, *H. influenzae*, *Staphylococcus* spp., and *Streptococcus* spp. are the more common cause of bacterial coinfections during clinical ILI (29).

Case studies documenting the role of HCWs in transmission of *S. pneumoniae* are absent, possibly because it is not an outbreak-associated disease (30). *B. pertussis* outbreaks in HCWs, however, occur commonly (31–35). In addition, occupational infection with *C. pneumoniae* and *M. pneumoniae* has been reported in HCWs (36, 37). In summary, bacterial pathogens certainly cause occupational infection in HCWs, and whatever the clinical significance, our research shows that N95 respirators protect HCWs from bacterial carriage. The highly significant difference in bacterial detection rates between the intervention arms, with more than double the rate in the medical arm compared with the N95 arm (mirroring the trend seen in the CRI outcome), suggests that bacterial colonization in the HCW setting can be prevented by N95 respirators, but not surgical masks. Of note, coinfection of viruses and bacteria in various combinations is common, and the same trend to protective efficacy of N95 respirators was seen against dual bacterial coinfections.

Our study used NAT to define influenza infection, which is a more reliable measure of true (and recent) infection than serology, but also resulted in a low rate of laboratory-confirmed viral infections and leaves our study underpowered to look at this outcome. The lack of demonstrable difference between confirmed viral infections could be because there is no difference, or because the study was underpowered for this outcome. This is therefore also a limitation of the study. During our study, A(H1N1)pdm09 activity in Beijing was waning (38). This explains the low rate of A (H1N1)pdm09 infection, with only four laboratory-confirmed cases identified. In the study by Loeb and coworkers (15), serologically defined influenza comprised most cases of influenza, but the study does not disclose the serologic status of those participants who had received influenza vaccination, who seem to have been included in the denominator for analysis. Defining influenza-seropositive vaccinated HCWs as influenza "cases" could result in misclassification error and bias, which makes serology a less ideal endpoint in such trials.

The follow-up period of 4 weeks was a limitation in our study because of the seasonality of different respiratory pathogens. A further limitation of our study was the uneven distribution of confounding variables, such as influenza vaccination and hand washing. We adjusted for this and found that the protective effect of N95 respirators remained statistically significant. Finally, compliance was measured by self-report, which is subject to bias. However, given the lower reported compliance in the N95 group, if noncompliance was higher than reported, this would drive the trial results toward the null, which means the true difference between the interventions may be greater than that observed.

TABLE 4. HAZARD RATIOS FROM MULTIVARIABLE COX PROPORTIONAL HAZARDS MODEL AFTER ADJUSTING FOR CLUSTERING EFFECT*

	Hazard Ratio (95% CI)	
Variables in the Model	CRI	Bacteria
N95 arm	0.39 (0.21–0.71)	0.40 (0.21–0.73)
Targeted N95 arm	0.70 (0.39–1.24)	0.70 (0.40–1.24)
Age	0.99 (0.97–1.02)	0.99 (0.97–1.01)
A(H1N1)pdm09 vaccination	0.87 (0.59–1.27)	0.88 (0.58–1.34)
Seasonal influenza vaccination	0.60 (0.38–0.94)	0.60 (0.37–0.98)
Hand washing	0.72 (0.49–1.07)	0.70 (0.44–1.10)
Staff, doctor	1.34 (0.87–2.05)	1.32 (0.84–2.06)

Definition of abbreviations: CI = confidence interval; CRI = clinical respiratory illness.

* Medical mask arm was used as referent category to estimate the hazard ratio for targeted and medical mask arms.

Acceptability of face mask use in developed country settings is lower than in Asian countries (39), and this limits the translation of the findings. We previously determined that running this trial in Australia would be unfeasible because of low compliance (40). However, the first proof of principle is to address the question of efficacy. The high acceptability of masks made China an ideal setting. Furthermore, many emerging infections have arisen in China and in Asia, so that the need for masks in clinical practice may be higher in such countries.

Our study found significantly higher reported adverse effects and discomfort of N95 respirators compared with the other two arms, consistent with other studies (16, 41). However, despite lower adherence in the N95 arm, the efficacy by intention-to-treat analysis was still higher than medical masks. A research question arising from this study is the cost-effectiveness of various mask policies, which was beyond the scope of this trial, but which we hope to address in future research. Our trial provides efficacy estimates, which are a required data input for cost-effectiveness analyses. In summary, this study adds evidence in favor of N95 respirators as respiratory protection for HCWs, and describes for the first time a differential rate of bacterial detection in the respiratory tract depending on level of respiratory protection. We are unaware of this being previously studied, and believe this warrants further research to understand the clinical significance of bacterial colonization in HCWs, and association with HCW symptomatology or transmission. The risks, benefits, and occupational health and safety implications of current guidelines on respiratory protection for HCWs, particularly during outbreaks of emerging infections for which other protective measures are unavailable, should be reviewed in light of our findings.

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