BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-012330
Article Type:	Research
Date Submitted by the Author:	18-Apr-2016
Complete List of Authors:	MacIntyre, Raina; University of New South Wales, Zhang, Yi; Institute for Infectious Disease and Endemic Disease Control, Beijing Center forDisease Prevention and Control (CDC) Chughtai, Abrar; Univesity of New South Wales, School of Public Health and Community Medicine Seale, Holly; University of New South Wales, School of Public Health and Community Medicine Zhang, Daitao; Institute for Infectious Disease and Endemic Disease Control, Beijing Center forDisease Prevention and Control (CDC) Chu, Yanhui; Xicheng District Center for Diseases Prevention and Control, Beijing , China Zhang, Haiyan ; Dongcheng District Center for Diseases Prevention and Control, Beijing, China Rahman, Bayzidur; University of New South Wales, School of Public Health and Community Medicine Wang, Quanyi; Institute for Infectious Disease and Endemic Disease Control, Beijing Center for disease prevention and control
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Infectious diseases
Keywords:	mask, influenza, Respiratory infections < THORACIC MEDICINE

Randomised controlled trial to examine medical mask use as source control for people with respiratory illness

Chandini Raina MacIntyre, Yi Zhang, Abrar Ahmad Chughtai, Holly Seale, Daitao Zhang, Yanhui Chu, Haiyan Zhang, Bayzidur Rahman, Quanyi Wang

School of Public Health and Community Medicine UNSW Medicine University of New South Wales Sydney Australia, The Beijing Centre for Disease Prevention and Control Beijing China, XiCheng district CDC Beijing China, Dongcheng district CDC Beijing China, Chandini Raina MacIntyre Professor and Head of School of Public Health and Community Medicine University of New South Wales, Yi Zhang Doctor The Beijing Centre for Disease Prevention and Control, Abrar Ahmad Chughtai Post doctorate Research Fellow University of New South Wales, Holly Seale Associate Lecturer University of New South Wales, Daitao Zhang, Doctor The Beijing Centre for Disease Prevention and Control, Yanhui Chu Doctor Xicheng District Center for Diseases Prevention and Control, Haiyan Zhang Doctor Dongcheng District Center for Diseases Prevention and Control, Bayzidur Rahman, Senior Lecturer University of New South Wales, Quanyi Wang Professor The Beijing Centre for Disease Prevention and Control

Corresponding author

Dr. Abrar Ahmad Chughtai

Level 2, Samuels Building

School of Public Health & Community Medicine, UNSW Medicine

University of New South Wales, Sydney 2052, Australia

Telephone: +61 (2) 9385 3129 Fax: +61 (2) 9313 6185

Email: doctorahmad75@gmail.com

ABSTRACT

Rationale: Medical masks are commonly used by sick individual with influenza like illness (ILI) to prevent spread of infections to others, but clinical efficacy data to inform this intervention are absent.

Objective: Determine whether medical mask use by sick individual with ILI protects well contacts from related respiratory infections.

Setting: Six major hospitals in two districts of Beijing, China

Design: Randomised controlled trial

Participants: 225 index cases with ILI

Intervention: Index cases with ILI were randomly allocated to medical mask and control arms. A post-hoc analysis was performed comparing outcomes among household members where index cases used a mask (mask group), with those who did not use a mask (no-mask group).

Main outcome measure: Primary endpoints measured in household contacts included: clinical respiratory illness, ILI and laboratory-confirmed viral respiratory infection.

Results:

In intention-to-treat analysis, rates of clinical respiratory illness (RR 0.61, 95% CI 0.18 to 2.07), ILI (RR 0.33, 95% CI 0.04 to 2.80) and laboratory confirmed viral infections (RR 0.59, 95% CI 0.01 to 36.74) were consistently lower in the mask arm compared to control, although not statistically significant. Comparison between the mask versus no-mask groups

showed a significantly protective effect against clinical respiratory illness (RR 0.24, 95% CI 0.06 to 0.93).

Conclusion:

The study was underpowered to detect a statistically significant difference in outcome in the intention-to-treat analysis, but showed benefit of mask use in the post-hoc analysis. This study indicates a potential benefit of medical masks for source control, but larger trials are needed to confirm efficacy.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. Masks were primarily designed as "source control", i.e. to be used by sick individuals to prevent transmission to others.
2. To date only one clinical trial has been conducted to see the efficacy of masks being "source control".
3. In this randomized clinical trial, the rates of all outcomes were consistently lower in the mask arm compared to control, although difference was not statistically significant.
4. Comparison between the mask versus no-mask groups in post-hoc analysis showed a significantly protective effect against clinical respiratory illness.
5. This study indicates a potential benefit of medical masks for source control, but larger trials are needed to confirm efficacy.

Trial registration: Australian New Zealand Clinical Trials Registry (ANZCTR), ACTRN12613000852752 (http://www.anzctr.org.au).

Funding source: This study was supported by UNSW Goldstar award.

INTRODUCTION

Medical masks are commonly used in healthcare settings for two main purposes: 1) by well healthcare workers (HCWs) to protect them from acquiring infection; and 2) by sick individuals to prevent transmission to others (source control) (1, 2). There are currently major gaps in our knowledge about the impact of masks on the transmission of respiratory infections (3). Most clinical trials have been focused on the protection of the well wearer, rather than on source control (3). Cloth and medical masks were originally developed as source control to prevent the spread of infection from the wearer in operating theatres (OTs) (4, 5), however their effectiveness in preventing surgical site infections is yet to be proven (6-8).

Although masks are also widely used in the community to prevent spread of infection from sick and infectious people (9-13), the majority of data on their use are observational and derived from outbreaks and pandemics. Among the 14 randomized controlled trials (RCTs) in healthcare and household/community settings to date (3), only one examined the role of masks as “source control” and was inconclusive (14). In the clinical trials in community settings, masks were either used by both sick patients (index cases as “source control”) and their household members (15-22) or used only by household members (16, 20, 21). No clear benefit of source control was identified in these studies. Laboratory studies generally support the use of medical masks to prevent spread of influenza and TB (23-25).

Mask use as source control in healthcare settings has now been included in standard infection control precautions during periods of increased respiratory infection activity in the community, yet there is no clinical efficacy evidence to support this recommendation. The

aim of this study was to determine whether medical mask use by people with influenza-like illness (ILI) protects well contacts from infection.

METHODS

Design

An RCT was conducted in fever clinics in six major hospitals in two districts of Beijing, China. The fever clinics are outpatient departments for the assessment and treatment of febrile patients. Recruitment was carried out over a period of 6 weeks. The recruitment of participants started on 18th November 2013 and completed on 20 January 2014. Adults who attended the fever clinic were screened by hospital staff to identify if they were eligible for the study. A study staff member approached eligible patients when they presented in the clinic and invited them to participate in the study. Recruited patients meeting the case definition of ILI (see below) were referred to as index cases, which is the first case in a potential chain of infection transmission.

Eligibility

Patients 18 years and older (index cases) with ILI (defined as fever ≥38ºC plus one respiratory symptom including cough, nasal congestion, runny nose, sore throat or sneezes) who attended a fever outpatient clinic during the study period, had no history of ILI amongst family members in the prior 14 days and who lived with at least two other people at home were recruited for the study. Patients who were unable or refused to give consent, had onset of symptoms >24 hours prior to recruitment, were admitted to hospital, resided in a household with less than two other people and have other ill household members at home were excluded from the study.

Randomisation

After providing informed consent, 225 index cases were included and randomly allocated to intervention (mask) and control (no mask) arms. A research team member (YZ) did the random allocation sequence and doctors enrolled the participants randomly to intervention and control arms. One hundred and twenty three index cases and 302 household contacts were included in the mask (source control) arm and 122 index cases and 295 household contacts were included in control arm (Figure 1). Cases and their household contacts were assigned together to either intervention or control arm.

Intervention

The mask or no mask intervention was applied to the index cases and respiratory illness was measured in household contacts. Index cases (patients with ILI) in the intervention arm wore a medical mask at home. Index cases were asked to wear a mask (3M 1817 surgical mask) whenever they were in the same room as a family member or a visitor to the household. They were allowed to remove their masks during meal times and while asleep. Index cases were shown how to wear the mask and instructed to wash their hands when donning and removing the mask. Index cases were provided with three masks per day for 7 days (21 masks in total). They were informed that they could cease wearing a mask once their symptoms resolved. Index cases in the control arm did not receive any intervention. Mask use by other household members was not required.

Outcome measures

Illness outcomes were measured in household contacts of the index cases. Primary endpoints measured in household contacts on a daily basis included: (1) clinical respiratory

illness (CRI), defined as two or more respiratory symptoms (cough, nasal congestion, runny nose, sore throat or sneezes) or one respiratory symptom and a systemic symptom (chill, lethargy, loss of appetite, abdominal pain, muscle or joint aches) ; (2) ILI, defined as fever ≥38ºC plus one respiratory symptom ; and (3) laboratory-confirmed viral respiratory infection, defined as detection of adenoviruses, human metapneumovirus, coronaviruses 229E/NL63 and OC43/HKU1, parainfluenzaviruses 1, 2 and 3, influenza viruses A and B, respiratory syncytial virus A and B, or rhinovirus A/B by nucleic acid testing (NAT) using a commercial multiplex polymerase chain reaction (PCR) (Seegen, Inc., Seoul, Korea) (26-28).

If any respiratory or systemic symptoms occurred in household members, index cases were instructed to notify the study coordinator. Symptomatic family members were asked to complete "sick follow up" questionnaires and anyone who met the CRI definition was tested for laboratory-confirmed viral respiratory infections. The study coordinator also performed twice-weekly follow-up phone calls to the families to actively ascertain incident illness in household members.

Patient involvement

We did not involve patients and their families in the design and conduct of the study. We have acknowledged the support of participants and the results will be published in open access journal.

Data collection and follow-up

At baseline: Detailed demographic, clinical details and household structure/demographic information was collected from all index cases and their household members. This included

age, sex, smoking history, comorbidities, medications, hand washing practices, influenza vaccination and normal practices around the use of masks.

Follow-up period (7 days): Each index case was asked to keep a diary to record activities, symptoms and daily temperatures for seven days. Symptoms in the family members were also recorded in the diary cards. Index cases in the intervention arm were also asked to document compliance with mask use (27, 28). Diary cards with tick boxes for mask use were given to each index case, and they were asked to carry them during the day.

Sample Collection and Laboratory Testing

Samples were collected from index patients at the time of recruitment and from symptomatic household members during follow-up. Household members were provided with an information sheet and written consent was sought before sampling. Only those household members who provided consent were swabbed. If the sick household member was aged <18years, consent was obtained from a parent or guardian.

Double rayon-tipped, plastic-shafted swabs were used to swab both tonsilar areas and the posterior pharyngeal wall of symptomatic subjects. The swabs were then transported immediately after collection to the Beijing CDC laboratories, or stored at 4ºC within 48 hrs if transport was delayed.

Viral DNA/RNA was extracted from each respiratory specimen using the Viral Gene-spin TM Kit (iNtRON Biotechnology, Inc., Seoul, Korea) according to the manufacturer's instructions. Reverse transcription was performed using the RevertAidTM First Strand cDNA Synthesis Kit (Fermentas, ON, Canada) to synthesize cDNA. Multiplex PCR was carried out using the Seeplex® RV12 Detection Kit (Seegen, Inc., Seoul, Korea) to detect adenoviruses, human

metapneumovirus, coronavirus 229E/NL63 and OC43/HKU1, parainfluenzaviruses 1, 2 or 3, influenza viruses A or B, respiratory syncytial virus A or B, and rhinovirus A/B. A mixture of 12 viral clones were used as a positive control template, and sterile deionized water was used as a negative control. Viral isolation by MDCK cell culture was undertaken for some of the influenza samples that were nucleic acid test (NAT) positive. NAT using a multiplex PCR was also done on the same DNA/RNA extract as used for the viral PCR (Seegen, Inc., Seoul, Korea) for Streptococcus pneumoniae, Mycoplasma pneumoniae, Bordetella pertussis, legionella, chlamydia and Haemophilus influenzae type B. Specimen processing, DNA/RNA extraction, PCR amplification, and PCR product analyses was conducted in different rooms to avoid cross-contamination.

Sample size

In this cluster randomized design, the household was the unit of randomization and the average household size was three people. Assuming the attack rate of CRI in the control households was 16-20% (based on the results of a previously published household mask trial) (16), with 5% significance level and 85% power, minimum relative risk of 0.5 (intervention/control), 385 participants were required in each arm, which was composed of 118 households and on average, three members per household. In this calculation, we assumed that the intracluster correlation coefficient was 0.1. An estimated 250 patients with ILI were recruited into the study to allow for possible index case dropout during the study.

Data analysis

Descriptive statistics were compared in mask and control arms and respiratory virus infection attack rates were quantified. Primary endpoints were analysed by intention to

treat across the study arms. Relative risks were calculated for the intervention. Kaplan-Meier survival curves were generated to compare the survival pattern of outcomes across mask and control arms. Differences between the survival curves were assessed through Log-rank test. Hazard ratios (HR) were calculated using a multivariable Cox proportional hazards model after adjusting for clustering and potential confounders. All variables in the initial model that were significant (P<0.25) were included in the univariate analysis. A backward elimination method was used to remove variables that did not have any confounding effect or were significantly associated with the outcome variable. We used a shared frailty Cox model to adjust for clustering by household.

A total of 36 index cases in the control arm also used a mask during the study period, so a post-hoc analysis was carried out to compare outcomes among household members of index cases who used a mask (hereafter "mask group"), with those of index cases who did not use a mask (hereafter "no-mask group"). Kaplan-Meier survival curves were generated to compare the survival pattern of outcomes across mask and no-mask groups. Hazard ratios were calculated using a multivariable Cox proportional hazards model as discussed before.

Ethics approval

Ethics approval was obtained from the Beijing Center for Disease Prevention and Control IRB and the Human Research Ethics Committee of the University of New South Wales (UNSW), Australia (HREC approval number HC13236).

RESULTS

A total of 245 index patients were randomised into the mask arm (n=123) or the control arm (n=122). The mask arm had on average 2.5 household contacts per index case (n=302), while

the control arm had 2.4 household contacts per index cases (n=295). Characteristics of index cases and household members are presented in table 1. Some differences were noted between arms, but most characteristics were generally similar between the two groups.

Table 2 shows the intention to treat analysis. CRI was reported in 4 (1.91/1000 person-days) household members in the mask arm, compared to 6 household members (2.95/1000 person-days) in the control arm (RR 0.65, 95% CI 0.18 to 2.29). Only 1 case (0.48/1000 person-days) of ILI was reported in the mask arm, compared to 3 cases (1.47/1000 person-days) in the control arm (RR 0.32, 95% CI 0.03 to 3.11). The rates of laboratory confirmed viral infection were similar among the household members and one case was reported in each arm (RR 0.97, 95% CI 0.06 to 15.5). The Kaplan-Meier curves showed no significant differences in the outcomes between two arms (P-value > 0.050) (Figure 2).

Multivariate analysis showed no association between mask use by the index cases and rates of infectious outcomes in household members (Table 3). Although the risks of CRI (RR 0.61, 95% CI 0.18 to 2.07), ILI (RR 0.33, 95% CI 0.04 to 2.80) and laboratory confirmed viral infections (RR 0.59, 95% CI 0.01 to 36.74) were lower in the masks arm, the difference was not statistically significant.

Tables 4 & 5 show an additional analysis comparing outcomes among household members of index cases using a mask (“mask group”), with those of index cases who did not use a mask (“no-mask group”). Overall, 159 index cases (65%) used a mask during the trial period including 36 subjects from the control arm. Three hundred and eighty seven household members were included in the mask group and 210 were included in the no-mask group. Rates of all outcomes were lower in the mask group, and CRI was significantly lower in the contacts of the mask group compared to the contacts of the no-mask group. The Kaplan-

Meier curves (Figure 3) showed a significant difference in the rate of CRI among the mask and no-mask groups (P- 0.020).

After adjusting for other factors, the risk of CRI was 76% lower in the contacts of the mask group (RR 0.24, 95% CI 0.06 to 0.93), compared to contacts of the no-mask group. Although the risks of ILI (RR 0.16, 95% CI 0.01 to 1.81) and laboratory-confirmed viral infections (RR 0.10, 95% CI 0.01 to 3.32) were also lower in the mask group, the difference was not statistically significant.

DISCUSSION

Masks are commonly recommended as source control for patients with respiratory infections to prevent the spread of infection to others (2, 3), but data on the clinical efficacy of this approach are sparse. This is the first clinical study of masks as source control. We did not find a significant benefit of medical masks as source control, but rates of secondary infections in household members were consistently lower in the mask arm compared to the control arm. The study may have been underpowered to detect a statistically significant difference. The additional analysis by actual mask use showed significantly lower rates of clinical infection in mask group compared to the no-mask group, suggesting larger trials should be conducted to further examine the efficacy of masks as source control.

Our findings are consistent with previous research in community and household settings, where the efficacy of masks as “source control” was measured. To date, only one RCT has been conducted in the community setting to examine the role of masks in preventing spread of infection from wearers (3). Canini et al. conducted an RCT in France during the 2008–2009 influenza season and randomised index patients into medical mask (52 households and 148

contacts) and control arms (53 households and 158 contacts). ILL was reported in 16.2% and 15.8% contacts in the intervention and control arms, respectively, and the difference was not statistically significant (OR 0.95, 95% CI: 0.44 to 2.05). The trial was concluded early due to low recruitment and the subsequent influenza A (H1N1)pdm09 pandemic (14). In addition, masks were also used by index cases in some community based RCTs with mixed interventions (15, 18). Cowling et al. conducted two RCTs in Hong Kong to examine to efficacy of masks, and index cases were randomised into medical mask, medical mask plus hand hygiene, hand hygiene and control arms. Both index cases and household members used masks. The rates of laboratory-confirmed influenza and ILI were the same in the intervention and control groups in the intention to treat analysis (15). However, in the second trial mask use with hand hygiene was protective in household contacts when the intervention was applied within 36 hours of onset of symptoms in the index case (OR 0.33, 95% CI, 0.13 to 0.87) (18).

Masks are not designed for respiratory protection and are commonly used in the healthcare setting to prevent spread of infections from the wearer, whether worn by a sick patient or well staff member (1, 3). One such use is the wearing of masks by well surgeons and other OT staff to protect patients from contamination during surgery. Previous studies examined the role of masks in the OT setting to examine spread of infections from surgeons and other OT staff to patients, however most of these studies were inconclusive (6, 8, 29, 30). Experimental studies have also demonstrated that the small amount of oral bacteria dispersed during normal breathing may not contaminate the operating field and the use of masks may not be necessary in the OT subject to the availability of proper ventilation (7). In contrast to this, some studies have supported the use of masks in the OT. Chamberlain and

Houang started an RCT in women having gynaecological surgery, which had to be discontinued in the initial phase because the rate of wound infection was found to be higher without mask use (31). The amount of bacteria falling on the operative field was significantly lower in a study, when the surgeon used a medical mask, compared to when the surgeon did not use a mask (32). Presumably, the exhaled pathogen load would be much higher in a sick patient compared to a well surgeon , and therefore the use of a mask for source control in sick patients may have more benefit than OT use of source control.

Despite a lack of evidence, most health organisations and countries recommend the use of masks by sick patients as source control (1, 2). Masks are used commonly by TB patients, although clinical trials have not been conducted for this indication. There is a need to conduct larger trials to confirm the suggestion of benefit in our study. If source control is effective in reducing hospital transmission of infection, this may have a practical benefit, to mitigate the problem of poor compliance with mask wearing among HCWs (3).

This study has some limitations. Sample size was small and the study was underpowered to detect a statistically significant difference in outcome in the intention-to-treat analysis. Post-hoc analysis however showed benefit of mask use and indicated a potential benefit of medical masks for source control. We measured self-reporting compliance using diary card which may subject to recall or other types of bias. Moreover compliance with the mask use was low and average masks use during the contact with family members was 51%.

Whilst mask use compliance is high among HCWs in some cultural settings (27, 28), it is low in many cultures, especially Western cultures (33), even during potentially fatal outbreaks such as SARS (34). Further, HCW compliance decreases with time during sustained outbreaks (27, 28). Therefore, reducing the infectiousness of source patients may be particularly

important in settings where HCW compliance with mask use is low. Compliance with any intervention for someone who is well and asymptomatic is far more challenging than compliance in people who are unwell (33), so source control may have an important role in hospital infection control. Reducing the transmission of respiratory pathogens by source patients could also have further benefits in the community in preventing transmission of infection to close contacts such as those in the same household, and should be studied further.

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COMPETING INTERESTS

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare that;

1. Professor C. Raina MacIntyre: Raina MacIntyre has held an Australian Research Council Linkage Grant with 3M as the industry partner, for investigator driven research. 3M have also contributed supplies of masks and respirators for investigator-driven clinical trials. She has received research grants and laboratory testing as in-kind support from Pfizer, GSK and Bio-CSL for investigator-driven research.

2. Dr Holly Seale had a NHMRC Australian based Public Health Training Fellowship at the time of the study (1012631). She has also received funding from vaccine manufacturers GSK, bio-CSL and Saniofi Pasteur for investigator-driven research and presentations.
3. Dr. Abrar Chughtai had testing of filtration of masks by 3M for PhD.

The remaining authors declare that they have no competing interests and have no non-financial interests that may be relevant to the submitted work."

ACKNOWLEDGEMENTS

Thanks to the staff at the Beijing Centre for Disease Control and hospitals staff. We also acknowledge the support of patients and their families. This study was supported by UNSW Goldstar award.

CONTRIBUTORSHIP STATEMENT

CRM: lead investigator, responsible for conception and design of the study, analysing data and writing the manuscript; Yi Zhang: YZ: implementation and database management, AAC: statistical analysis and drafting of manuscript; HS, DZ, YC, HZ: recruitment and training, manuscript revision, Bayzidur Rahman: contributed to the statistical analysis and revision of manuscript, QW: implementation, contribution to design, analysis and drafting of paper.

TRANSPARENCY DECLARATION

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA SHARING STATEMENT

No additional data available

FIGURE LEGENDS

Figure1. Consort diagram of recruitment and follow-up

Figure 2: Survival curves for medical mask vs control arms

Figure 3: Survival curves for mask vs no mask group

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Table 1: Demographic and other characteristics of the index cases and household members

Variable	Mask arm (% and 95% CI)	Control arm (% and 95% CI)
Index case (number)	**123**	**122**
Gender (male)	56/123 45.5% (37.0% to 54.3)	45/122 36.9% (28.8% to 45.7%)
Age (mean)	40.2 (37.6 to 42.8)	39.7 (37.3 to 42.0)
Education (Under/postgraduate)	78/123 63.4% (54.6%-71.4%)	74/122 60.7% (51.8 to 68.9%)
Smoker (Current/Ex)	29/123 23.6% (16.9% to 31.8%)	26/122 21.3% (15.0% to 29.4%)
Pre-existing illness*	21/123 17.1% (16.2% to 31.0%)	16/122 13.1% (8.2% to 20.2%)
Influenza vaccination (Yes)	5/123 4.1% (1.7% to 9.2%)	5/122 4.1% (1.8% to 9.2%)
Hand washing (most/all times)	98/123 79.7% (71.7% to 85.8%)	109/122 89.3% (82.6% to 93.7%)
Average hour of home stay†	16.6 (15.9 to 17.3)	16.6 (15.9 to 17.3)
Average hour of contact†	10.4 (9.2 to 11.5)	11.1 (10.0 to 12.1)
Average hour mask wearing†	4.4 (3.9 to 4.9)	1.4 (0.9 t0 1.8)
Household (members)	**302**	**295**
Number of house hold per arm	2.5	2.4
Gender (male)	149/302 49.0% (43.4% to 24.6%)	168/295 57.3% (51.6% to 62.9%)
Influenza vaccination (Yes) ‡	22/298 7.4% (4.9% to 10.9%)	30/285 10.5% (7.1% to 14.6%)
Age (mean)	38.3 (36.0 to 40.5)	36.4 (34.1 to 38.8)

* *Includes asthma, chronic obstructive pulmonary disease, diabetes, ischemic heart disease, immune-compromised and others*

† *Variable was created by taking average hours over the trial period.*

‡ *Missing data for 14 cases.*

Table 2: Number and proportion of household members reporting primary outcomes, by randomization arm and intention-to-treat analysis (n=597)*

	Clinical respiratory illness (CRI) No (rate person-days)	RR (95% CI)	Influenza like illness (ILI) No (rate person-days)		Laboratory confirmed viruses No (rate person-days)	RR (95% CI)
Mask arm	4/2098 (1.91/1000)	0.65 (0.18-2.29)	1/2098 (0.48/1000)	0.32 (0.03-3.11)	1/2098 (0.48/1000)	0.97 (0.06-15.5)
Control arm	6/2036 (2.95/1000)	Ref	3/2036 (1.47/1000)	Ref	1/2036 (0.49/1000)	Ref

* House hold members (mask arm 302 and control arm 295)

Table 3: Hazard ratios from multivariable cox proportional hazards model for household members in masks vs. control arms (n=597)*

	Clinical respiratory illness (CRI) HR (95% CI)	Influenza like illness (ILI) HR (95% CI)	Laboratory confirmed viruses HR (95% CI)
Masks arm (Index case)	0.61 (0.18-2.07)	0.33 (0.04-2.80)	0.59 (0.01-36.74)
Control arm (Index case)	Ref	Ref	Ref
Male (Index case)	0.91 (0.26-3.19)	1.08 (0.13-8.75)	0.87 (0.01-60.75)
Age (Index case)	1.03 (1.00-1.06)	1.04 (0.98-1.10)	1.01 (0.98-1.04)
Hand washing (Index case)	0.91 (0.32-2.80)	2.61 (0.23-29.58)	0.20 (0.04-0.95)
Male (Household)	3.74 (0.99-14.09)	2.23 (0.45-10.99)	1.72 (0.17-17.05)
Age (Household)	1.03 (1.01-1.05)	1.02 (0.99-1.04)	1.08 (1.05-1.01)
Vaccination (Household)	0.68 (0.25-1.85)	0.40 (0.08-1.67)	1.61 (0.97-2.66)

* House hold members (mask arm 302 and control arm 295)

Table 4: Number and proportion of participants reporting primary outcomes, by masks vs. no-mask groups (n=597)*

	Clinical respiratory illness (CRI) No (rate person-days)	*RR*	Influenza like illness (ILI) No (rate person-days)	*RR*	Laboratory confirmed viruses No (rate person-days)	*RR*†
Mask group	3/2694 (1.11/1000)	0.23 (0.06-0.88)	1/2694 (0.37/1000)	0.18 (0.02-1.71)	0/2694 (0/1000)	0.11 (0.01-4.40)
No mask group	7/1440 (4.86/1000)	Ref	3/1440 (2.08/1000)	Ref	2/1440 (0.70/1000)	Ref

* Household members (mask group 387 and no-mask group 210)

† Calculated through Cox PH methods

Table 5: Hazard ratios from multivariable cox proportional hazards model for masks vs. no masks groups (no randomisation) (n=597)*

	Clinical respiratory illness (CRI) HR (95% CI)	Influenza like illness (ILI) HR (95% CI)	Laboratory confirmed viruses HR (95% CI)
Masks group (Index case)	**0.24 (0.06-0.93)**	0.16 (0.01 – 1.81)	0.10 (0.01 – 3.32)
No mask group (Index case)	Ref	Ref	Ref
Male (Index case)	0.97 (0.28-3.37)	1.46 (0.20-10.90)	0.60 (0.03-12.31)
Age (Index case)	1.02 (0.99-1.06)	1.03 (0.97-1.08)	1.01 (0.92-1.01)
Hand washing (Index case)	0.98 (0.33-2.92)	2.94 (0.34-25.58)	0.19 (0.02-1.85)
Male (Household)	3.54 (0.93-13.50)	2.17 (0.48-9.80)	1.63 (0.07-36.20)
Age (Household)	1.03 (1.01-1.05)	1.01 (0.99-1.04)	1.08 (0.98-1.19)
Vaccination (Household)	0.66 (0.21-2.07)	0.27 (0.05-1.51)	1.47 (0.03-66.53)

* Household members (mask group 387 and no-mask group 210)

Figure1. Consort Diagram of recruitment and follow-up

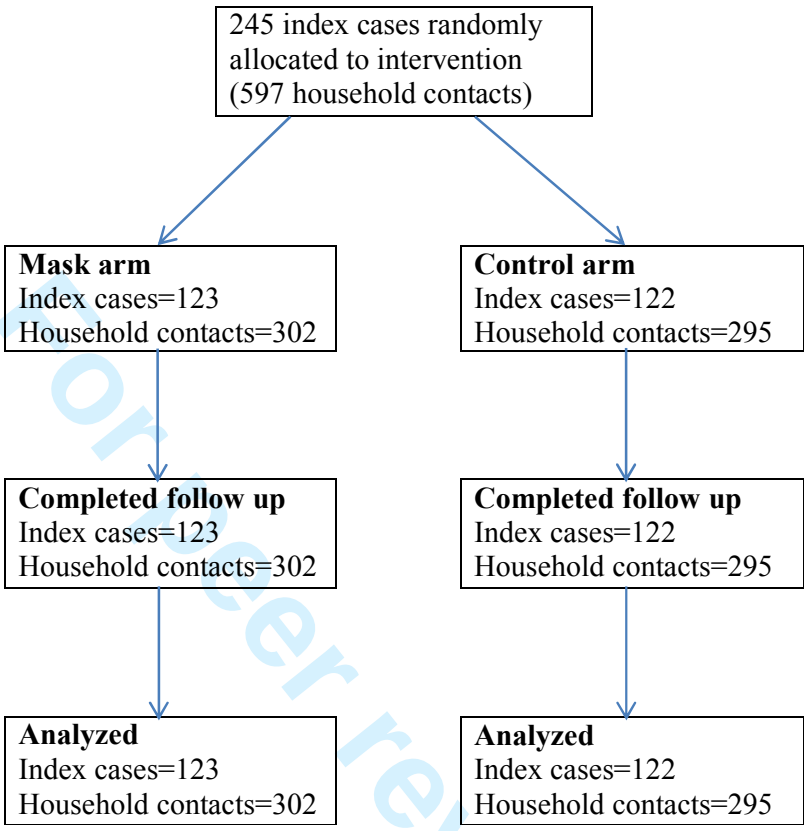
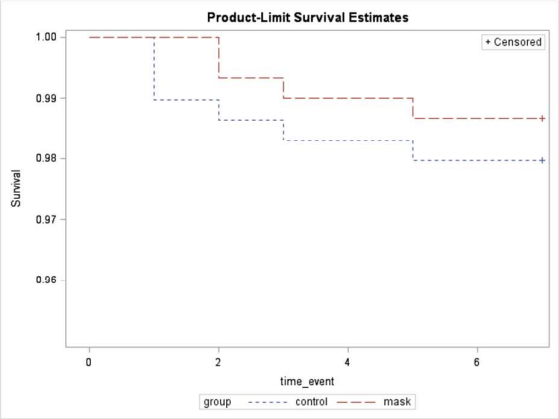
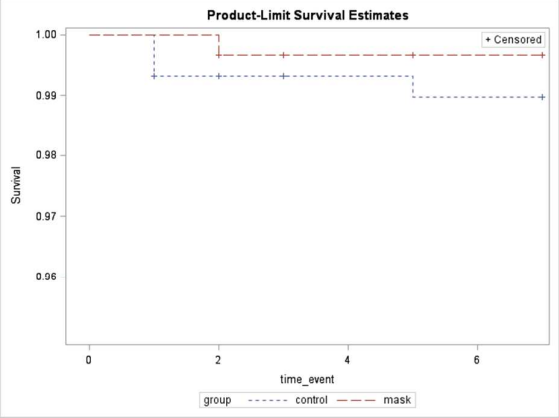


Figure 2: Survival curves for medical mask vs control arms

CRI



ILI



Virus

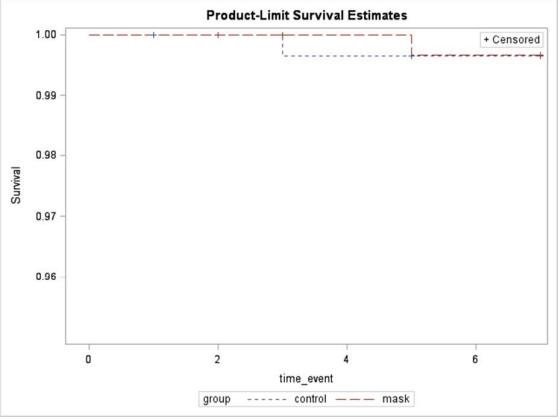
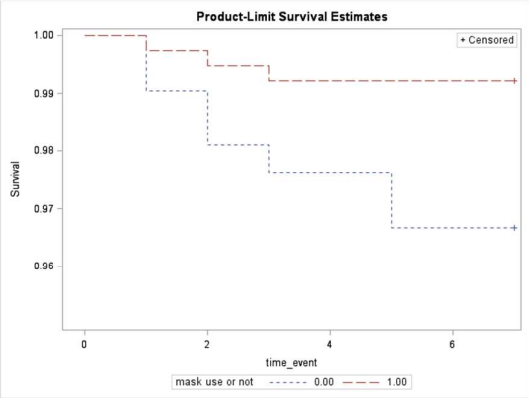
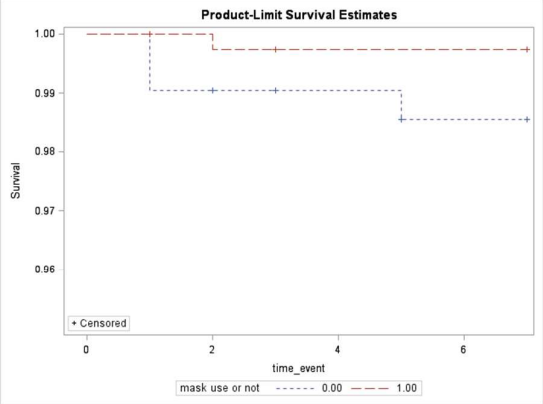


Figure 3: Survival curves for mask vs no mask group

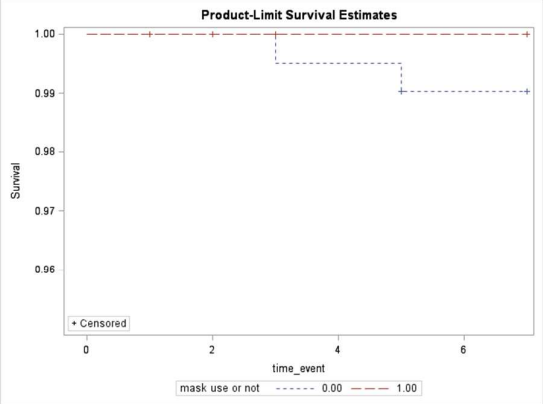
CRI



ILI



Virus



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6-7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	NA

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9-10
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10
	13b	For each group, losses and exclusions after randomisation, together with reasons	10
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	5
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	22
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	23
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	23
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	23
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	24
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	3

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Cluster randomised controlled trial to examine medical mask use as source control for people with respiratory illness

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-012330.R1
Article Type:	Research
Date Submitted by the Author:	12-Aug-2016
Complete List of Authors:	MacIntyre, Raina; University of New South Wales, Zhang, Yi; Institute for Infectious Disease and Endemic Disease Control, Beijing Center forDisease Prevention and Control (CDC) Chughtai, Abrar; Univesity of New South Wales, School of Public Health and Community Medicine Seale, Holly; University of New South Wales, School of Public Health and Community Medicine Zhang, Daitao; Institute for Infectious Disease and Endemic Disease Control, Beijing Center forDisease Prevention and Control (CDC) Chu, Yanhui; Xicheng District Center for Diseases Prevention and Control, Beijing , China Zhang, Haiyan ; Dongcheng District Center for Diseases Prevention and Control, Beijing, China Rahman, Bayzidur; University of New South Wales, School of Public Health and Community Medicine Wang, Quanyi; Institute for Infectious Disease and Endemic Disease Control, Beijing Center for disease prevention and control
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Infectious diseases
Keywords:	Mask, Influenza, Infection control < INFECTIOUS DISEASES

Cluster randomised controlled trial to examine medical mask use as source control for people with respiratory illness

Chandini Raina MacIntyre, Yi Zhang, Abrar Ahmad Chughtai, Holly Seale, Daitao Zhang, Yanhui Chu, Haiyan Zhang, Bayzidur Rahman, Quanyi Wang

School of Public Health and Community Medicine UNSW Medicine University of New South Wales Sydney Australia and College of Public Service & Community Solutions, Arizona State University, Phoenix, Arizona, United States, The Beijing Centre for Disease Prevention and Control Beijing China, XiCheng district CDC Beijing China, Dongcheng district CDC Beijing China, Chandini Raina MacIntyre Professor and Head of School of Public Health and Community Medicine University of New South Wales, Yi Zhang Doctor The Beijing Centre for Disease Prevention and Control, Abrar Ahmad Chughtai Post doctorate Research Fellow University of New South Wales, Holly Seale Associate Lecturer University of New South Wales, Daitao Zhang, Doctor The Beijing Centre for Disease Prevention and Control, Yanhui Chu Doctor Xicheng District Center for Diseases Prevention and Control, Haiyan Zhang Doctor Dongcheng District Center for Diseases Prevention and Control, Bayzidur Rahman, Senior Lecturer University of New South Wales, Quanyi Wang Professor The Beijing Centre for Disease Prevention and Control

Corresponding author

Dr. Abrar Ahmad Chughtai

Level 2, Samuels Building, School of Public Health & Community Medicine, UNSW Medicine University of New South Wales, Sydney 2052, Australia

Telephone: +61 (2) 9385 3129 Fax: +61 (2) 9313 6185

Email: doctorahmad75@gmail.com

ABSTRACT

Rationale: Medical masks are commonly used by sick individual with influenza like illness (ILI) to prevent spread of infections to others, but clinical efficacy data are absent.

Objective: Determine whether medical mask use by sick individuals with ILI protects well contacts from related respiratory infections.

Setting: Six major hospitals in two districts of Beijing, China

Design: Cluster randomised controlled trial

Participants: 245 index cases with ILI

Intervention: Index cases with ILI were randomly allocated to medical mask and control arms. A total of 43 index cases in the control arm also used a mask during the study period a post-hoc analysis was performed comparing outcomes among household members where index cases used a mask (mask group), with those who did not use a mask (no-mask group).

Main outcome measure: Primary outcomes were clinical respiratory illness measured in family members; ILI measured in family members; and laboratory-confirmed viral or bacterial respiratory infection, measured in family members

Results:

In intention-to-treat analysis, rates of clinical respiratory illness (RR 0.61, 95% CI 0.18 to 2.13), ILI (RR 0.32, 95% CI 0.03 to 3.13) and laboratory confirmed viral infections (RR 0.97, 95% CI 0.06 to 15.54) were consistently lower in the mask arm compared to control, although not statistically significant. A post-hoc comparison between the mask versus no-

mask groups showed a significantly protective effect against clinical respiratory illness (RR 0.22, 95% CI 0.06 to 0.86), but not against ILI (RR 0.18, 95% CI 0.02 – 1.73) and laboratory confirmed viral infection (RR 0.11, 95% CI 0.01 – 4.40).

Conclusion:

The study was underpowered to detect a statistically significant difference in outcome in the intention-to-treat analysis, but showed benefit of mask use in the post-hoc analysis. This study indicates a potential benefit of medical masks for source control, but larger trials are needed to confirm efficacy.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths

1. We conducted a randomised control trial to examine the efficacy of masks as "source control". .
2. The rates of all outcomes were consistently lower in the mask arm compared to control, although difference was not statistically significant by intention to treat analysis.
3. Comparison between the mask versus no-mask groups in post-hoc analysis showed a significantly protective effect against clinical respiratory illness, indicating a potential benefit of medical masks for source control.

Limitations

4. The sample size was small and the study may have been underpowered to detect a statistically significant difference in outcome in the intention-to-treat analysis.
5. Removal of masks in the intervention arm during meal times may have reduced efficacy and biased the results toward the null.

Trial registration: Australian New Zealand Clinical Trials Registry (ANZCTR), ACTRN12613000852752 (http://www.anzctr.org.au).

Funding source: This study was supported by UNSW Goldstar award.

INTRODUCTION

Medical masks are commonly used in healthcare settings for two main purposes: 1) by well healthcare workers (HCWs) to protect them from splash and spray of blood and body fluids; and 2) by sick individuals to prevent transmission to others (source control) (1, 2). There are currently major gaps in our knowledge about the impact of masks on the transmission of respiratory infections (3). Most clinical trials have been focused on the protection of the well wearer, rather than on source control (3). Cloth and medical masks were originally developed as source control to prevent the spread of infection from the wearer in operating theatres (OTs) (4, 5), however their effectiveness in preventing surgical site infections is yet to be proven (6-8).

Although masks are also widely used in the community to prevent spread of infection from sick and infectious people (9-13), the majority of data on their use are observational and derived from outbreaks and pandemics. Among the 9 randomized controlled trials (RCTs) in household and community settings to date (3), only one examined the role of masks as "source control" and was inconclusive (14). In other clinical trials, masks were either used by both sick patients (index cases as "source control") and their household members (15-17) or used only by household members (18-20). Most of these studies failed to show any efficacy of mask use in preventing spread of infections from the sick individuals.

Masks are also used to prevent surgical site infections in the operating theatre (OT) (3), although most studies failed to show any efficacy against this indication (6-8, 21). Only one clinical trial reported high infection rates after surgery if masks were not used by the surgeon in the OT (22). Among the five clinical trials in the healthcare setting to test the efficacy of masks/ respirators as respiratory protection (3), none examined the use of masks

as source control. Laboratory studies generally support the use of medical masks to prevent spread of infections from influenza and TB patients to their contacts (23-25).

Mask use as source control in healthcare settings has now been included in standard infection control precautions during periods of increased respiratory infection activity in the community, yet there is no clinical efficacy evidence to support this recommendation. The aim of this study was to determine whether medical mask use by people in a community setting with influenza-like illness (ILI) protects well contacts from infection.

METHODS

Design

An RCT was conducted in fever clinics in six major hospitals in two districts of Beijing, China. The fever clinics are outpatient departments for the assessment and treatment of febrile patients. Recruitment was carried out over a period of 6 weeks. The recruitment of participants started on 18th November 2013 and completed on 20 January 2014. Adults who attended the fever clinic were screened by hospital staff to identify if they were eligible for the study. A study staff member approached eligible patients when they presented in the clinic and invited them to participate in the study. Recruited patients meeting the case definition of ILI (see below) were referred to as index cases, which is the first case in a potential chain of infection transmission.

Eligibility

Patients 18 years and older (index cases) with ILI (defined as fever ≥38ºC plus one respiratory symptom including cough, nasal congestion, runny nose, sore throat or sneezes)

who attended a fever outpatient clinic during the study period, had no history of ILI amongst family members in the prior 14 days and who lived with at least two other people at home were recruited for the study. ILI was used as a selection criterion to achieve high specificity for index cases. Patients who were unable or refused to give consent, had onset of symptoms >24 hours prior to recruitment, were admitted to hospital, resided in a household with less than two other people and have other ill household members at home were excluded from the study.

Randomisation

After providing informed consent, 245 index cases were included and randomly allocated to intervention (mask) and control (no mask) arms. A research team member (YZ) did the random allocation sequence using Microsoft Excel and doctors enrolled the participants randomly to intervention and control arms. Patients had an equal chance to be in the either intervention or control arm. One hundred and twenty three index cases and 302 household contacts were included in the mask (source control) arm and 122 index cases and 295 household contacts were included in control arm (Figure 1). Cases and their household contacts were assigned together as a cluster to either intervention or control arm.

Intervention

The mask or no mask intervention was applied to the index cases and respiratory illness was measured in household contacts. Index cases (patients with ILI) in the intervention arm wore a medical mask at home. Index cases were asked to wear a mask (3M 1817 surgical mask) whenever they were in the same room as a family member or a visitor to the household. They were allowed to remove their masks during meal times and while asleep. Index cases

were shown how to wear the mask and instructed to wash their hands when donning and removing the mask. Index cases were provided with three masks per day for 7 days (21 masks in total). They were informed that they could cease wearing a mask once their symptoms resolved. Index cases in the control arm did not receive any intervention. Mask use by other household members was not required.

Outcome measures

Illness outcomes were measured in household contacts of the index cases. Primary endpoints measured in household contacts included: (1) clinical respiratory illness (CRI), defined as two or more respiratory symptoms (cough, nasal congestion, runny nose, sore throat or sneezes) or one respiratory symptom and a systemic symptom (chill, lethargy, loss of appetite, abdominal pain, muscle or joint aches) ; (2) ILI, defined as fever ≥38ºC plus one respiratory symptom ; and (3) laboratory-confirmed viral respiratory infection, defined as detection of adenoviruses, human metapneumovirus, coronaviruses 229E/NL63 and OC43/HKU1, parainfluenzaviruses 1, 2 and 3, influenza viruses A and B, respiratory syncytial virus A and B, or rhinovirus A/B by nucleic acid testing (NAT) using a commercial multiplex polymerase chain reaction (PCR) (Seegen, Inc., Seoul, Korea) (26-28).

If any respiratory or systemic symptoms occurred in household members, index cases were instructed to notify the study coordinator. Symptomatic family members were asked to complete "sick follow up" questionnaires and anyone who met the CRI definition was tested for laboratory-confirmed viral respiratory infections. The study coordinator also performed twice-weekly follow-up phone calls to the families to actively ascertain incident illness in household members.

Data collection and follow-up

At baseline: Detailed demographic, clinical details and household structure/demographic information was collected from all index cases and their household members. This included age, sex, smoking history, comorbidities, medications, hand washing practices, influenza vaccination and normal practices around the use of masks.

Follow-up period (7 days): Each index case was asked to keep a diary to record activities, symptoms and daily temperatures for seven days. Symptoms in the family members were also recorded in the diary cards and index cases were asked to report any symptom. The index cases were asked to contact the study coordinator if any of the following symptoms appeared in household members: cough, nasal congestion, runny nose, sore throat, sneezes, chill, lethargy, loss of appetite, abdominal pain and muscle or joint aches. The study coordinator then assessed the household member and completed a follow-up survey. Samples obtained from all symptomatic cases. All index cases in the intervention and control arms were also asked to document compliance with mask use (27, 28). Diary cards to record mask use were given to each index case, and they were asked to carry them during the day. Diary cards were returned to the investigators at the end of the study. Staff in the district CDC also contacted index cases via telephone on every alternate day to check whether any household member developed symptoms. Assessors were not blinded, because the intervention (mask wearing) is visible. However, laboratory testing was blinded.

Sample Collection and Laboratory Testing

Samples were collected from index patients at the time of recruitment and from symptomatic household members during follow-up. Household members were provided

with an information sheet and written consent was sought before sampling. Only those household members who provided consent were swabbed. If the sick household member was aged <18years, consent was obtained from a parent or guardian. Swabs were taken at the home by trained investigators.

Double rayon-tipped, plastic-shafted swabs were used to swab both tonsilar areas and the posterior pharyngeal wall of symptomatic subjects. The swabs were then transported immediately after collection to the Beijing CDC laboratories, or stored at 4ºC within 48 hrs if transport was delayed.

Viral DNA/RNA was extracted from each respiratory specimen using the Viral Gene-spin TM Kit (iNtRON Biotechnology, Inc., Seoul, Korea) according to the manufacturer's instructions. Reverse transcription was performed using the RevertAidTM First Strand cDNA Synthesis Kit (Fermentas, ON, Canada) to synthesize cDNA. Multiplex PCR was carried out using the Seeplex® RV12 Detection Kit (Seegen, Inc., Seoul, Korea) to detect adenoviruses, human metapneumovirus, coronavirus 229E/NL63 and OC43/HKU1, parainfluenzaviruses 1, 2 or 3, influenza viruses A or B, respiratory syncytial virus A or B, and rhinovirus A/B. A mixture of 12 viral clones were used as a positive control template, and sterile deionized water was used as a negative control. Viral isolation by MDCK cell culture was undertaken for some of the influenza samples that were nucleic acid test (NAT) positive. NAT using a multiplex PCR was also done on the same DNA/RNA extract as used for the viral PCR (Seegen, Inc., Seoul, Korea) for Streptococcus pneumoniae, Mycoplasma pneumoniae, Bordetella pertussis, legionella, chlamydia and Haemophilus influenzae type B. Specimen processing, DNA/RNA extraction, PCR amplification, and PCR product analyses was conducted in different rooms to avoid cross-contamination.

Sample size

In this cluster randomized design, the household was the unit of randomization and the average household size was three people. Assuming the attack rate of CRI in the control households was 16-20% (based on the results of a previously published household mask trial) (18), with 5% significance level and 85% power, minimum relative risk of 0.5 (intervention/control), 385 participants were required in each arm, which was composed of 118 households and on average, three members per household. In this calculation, we assumed that the intracluster correlation coefficient (ICC) was 0.1. An estimated 250 patients with ILI were recruited into the study to allow for possible index case dropout during the study.

Data analysis

Descriptive statistics were compared in mask and control arms and respiratory virus infection attack rates were quantified. Data from the diary cards were used to calculate person-days of infection incidence. Primary endpoints were analysed by intention to treat across the study arms and ICC for clustering by household was estimated using clchi2 command in Stata (29). Relative risks were calculated for the mask group. Kaplan-Meier survival curves were generated to compare the survival pattern of outcomes across mask and control arms. Differences between the survival curves were assessed through Log-rank test. The analyses were conducted in individual level and hazard ratios (HR) were calculated using Cox proportional hazards model after adjusting for clustering by household by adding a shared frailty to the model. Due to very few outcome events encountered a multivariable Cox model was not appropriate. We checked the effect of individual potential confounders on the outcome variable fitting univariable Cox models. Because there are 10 cases of CRI,

we included this variable in a multivariable cluster adjusted Cox model. Multivariate analyses were not performed for ILI and laboratory confirmed influenza because of low numbers.

A total of 43 index cases in the control arm also used a mask during the study period and 7 index cases in the masks arm did not use a mask, so a post-hoc sensitivity analysis was carried out to compare outcomes among household members of index cases who used a mask (hereafter "mask group"), with those of index cases who did not use a mask (hereafter "no-mask group"). All statistical analyses were conducted using Stata version 13.

Ethics approval

Ethics approval was obtained from the Beijing Center for Disease Prevention and Control IRB and the Human Research Ethics Committee of the University of New South Wales (UNSW), Australia (HREC approval number HC13236).

RESULTS

A total of 245 index patients were randomised into the mask arm (n=123) or the control arm (n=122). The mask arm had on average 2.5 household contacts per index case (n=302), while the control arm had 2.4 household contacts per index cases (n=295). Characteristics of index cases and household members are presented in table 1. Some differences were noted between arms, but most characteristics, including medication use (data not shown), were generally similar between the two groups. Viruses were isolated from 60% (146/245) index cases. Influenza was the most common virus isolated from 115 (47%) cases - Influenza A - 100, Influenza B - 11 and Influenza A&B - 4. Other viruses isolated from index cases were,

rhinovirus (14), NL63 (12) and C229E (7). More than one virus was isolated in 48 (20%) index cases, including 17 coinfections with influenza.

Table 2 shows the intention to treat analysis. CRI was reported in 4 (1.91/1000 person-days) household members in the mask arm, compared to 6 household members (2.95/1000 person-days) in the control arm (RR 0.65, 95% CI 0.18 to 2.29). Only 1 case (0.48/1000 person-days) of ILI was reported in the mask arm, compared to 3 cases (1.47/1000 person-days) in the control arm (RR 0.32, 95% CI 0.03 to 3.11). Two laboratory confirmed infections were identified among symptomatic household members – only one had the same infection (influenza H1N1) as the respective index case. Rhinovirus was isolated from other household member however no pathogen was isolated from respective index case. The rates of laboratory confirmed viral infection were similar among the household members, with one case was reported in each arm (RR 0.97, 95% CI 0.06 to 15.5). The Kaplan-Meier curves showed no significant differences in the outcomes between two arms (P-value > 0.050) (Figure 2).

In a univariable Cox model only the age of household contact was significantly associated with the CRI (Table 3). There was no association between mask use by the index cases and rates of infectious outcomes in household members (Table 3). Although the risks of CRI (RR 0.61, 95% CI 0.18 to 2.13), ILI (RR 0.32, 95% CI 0.03 to 3.13) and laboratory confirmed viral infections (RR 0.97, 95% CI 0.06 to 15.54) were lower in the mask arm, the difference was not statistically significant.

Tables 4 & 5 show a sensitivity analysis comparing outcomes among household members of index cases using a mask (“mask group”), with those of index cases who did not use a mask (“no-mask group”). Overall, 159 index cases (65%) used a mask during the trial period

including 43 subjects from the control arm. Three hundred and eighty seven household members were included in the mask group and 210 were included in the no-mask group. Rates of all outcomes were lower in the mask group, and CRI was significantly lower in the contacts of the mask group compared to the contacts of the no-mask group. The Kaplan-Meier curves (Figure 3) showed a significant difference in the rate of CRI among the mask and no-mask groups (P- 0.020).

After adjusting for the age of household contacts, the risk of CRI was 78% lower in the contacts of the mask group (RR 0.22, 95% CI 0.06 to 0.86), compared to contacts of the no-mask group. Although the risks of ILI (RR 0.18, 95% CI 0.02 to 1.73) and laboratory-confirmed viral infections (RR 0.11, 95% CI 0.01 to 4.40) were also lower in the mask group, the difference was not statistically significant.

DISCUSSION

Masks are commonly recommended as source control for patients with respiratory infections to prevent the spread of infection to others (2, 3), but data on the clinical efficacy of this approach are sparse. We did not find a significant benefit of medical masks as source control, but rates of secondary infections in household members were consistently lower in the mask arm compared to the control arm. The study may have been underpowered to detect a statistically significant difference. The additional analysis by actual mask use showed significantly lower rates of clinical infection in mask group compared to the no-mask group, suggesting larger trials should be conducted to further examine the efficacy of masks as source control.

Our findings are consistent with previous research in community and household settings, where the efficacy of masks as "source control" was measured. To date, only one RCT has been conducted in the community setting to examine the role of masks in preventing spread of infection from wearers (3). Canini et al. conducted an RCT in France during the 2008–2009 influenza season and randomised index patients into medical mask (52 households and 148 contacts) and control arms (53 households and 158 contacts). ILL was reported in 16.2% and 15.8% contacts in the intervention and control arms, respectively, and the difference was not statistically significant (OR 0.95, 95% CI: 0.44 to 2.05). The trial was concluded early due to low recruitment and the subsequent influenza A (H1N1)pdm09 pandemic (14). In addition, masks were also used by both index cases and household members in some community based RCTs with mixed interventions (15, 16). Cowling et al. conducted two RCTs in Hong Kong to examine the efficacy of masks, and index cases were randomised into medical mask, medical mask plus hand hygiene, hand hygiene and control arms. Both index cases and household members used masks. The rates of laboratory-confirmed influenza and ILI were the same in the intervention and control groups in the intention to treat analysis (15). However, in the second trial mask use with hand hygiene was protective in household contacts when the intervention was applied within 36 hours of onset of symptoms in the index case (OR 0.33, 95% CI, 0.13 to 0.87) (16). As masks were used by both sick patients and their household members in these studies, the effect of mask being "source control" is more difficult to precisely quantify.

Masks are not designed for respiratory protection and are commonly used in the healthcare setting to prevent spread of infections from the wearer, whether worn by a sick patient or well staff member (1, 3). One such use is the wearing of masks by well surgeons and other

OT staff to protect patients from contamination during surgery. Presumably, the exhaled pathogen load would be much higher in a sick patient compared to a well surgeon, and therefore the use of a mask for source control in sick patients may have more benefit than OT use of source control.

This study has some limitations. The sample size was small and the study may have been underpowered to detect a statistically significant difference in outcome in the intention-to-treat analysis. Post-hoc analysis however, showed a potential benefit of medical masks for source control. It is possible that infection transmission may have occurred during meal times (when patients were not required to wear a mask). This would have the effect of biasing the results toward the null. In the sample size calculations, we assumed 16-20% attack rate of CRI in the control arm, based on the results of a previously published household mask trial (18). However the secondary attack rates were much lower in this study which might be due to testing only symptomatic cases.

In a univariable Cox model only the age of household contact was significantly associated with the CRI. All other variables were uniformly distributed among the study arms so we only adjusted for age of household contact in the analysis of CRI as an outcome. Multivariate analyses were not performed for ILI and laboratory confirmed influenza. However some variables may have impact on the number of events. For example the rates of hand hygiene were higher among the "control" arm compared to the mask arm (109/122, 89.3% vs. 98/123, 79.7%) which may have had an impact on the number of outcome events. Due to low event rates and non-significant difference of hand hygiene among the two arms, we did not adjust for hand hygiene in any analysis. Further, inclusion of hand hygiene in the model did not change the HR. Finally, post-hoc analyses are potentially biased due to loss of

randomisation and it was added as a sensitivity analysis in this study because of deviations from protocol in mask wearing.

Despite a lack of evidence, most health organisations and countries recommend the use of masks by sick patients as source control (1, 2). Masks are used commonly by TB patients, although clinical trials have not been conducted for this indication. There is a need to conduct larger trials to confirm the suggestion of benefit in our study. If source control is effective in reducing hospital transmission of infection, this may have a practical benefit to mitigate the problem of poor compliance with mask wearing among well HCWs (3). Compliance with any intervention for someone who is well and asymptomatic is far more challenging than compliance in people who are unwell (30), so source control may have an important role in hospital infection control. Reducing the transmission of respiratory pathogens by source patients could also have further benefits in the community in preventing transmission of infection to close contacts such as those in the same household, and should be studied further.

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COMPETING INTERESTS

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare that;

1. Professor C. Raina MacIntyre: Raina MacIntyre has held an Australian Research Council Linkage Grant with 3M as the industry partner, for investigator driven research. 3M have also contributed supplies of masks and respirators for investigator-driven clinical trials. She has received research grants and laboratory testing as in-kind support from Pfizer, GSK and Bio-CSL for investigator-driven research.
2. Dr Holly Seale had a NHMRC Australian based Public Health Training Fellowship at the time of the study (1012631). She has also received funding from vaccine manufacturers GSK, bio-CSL and Saniofi Pasteur for investigator-driven research and presentations.
3. Dr. Abrar Chughtai had testing of filtration of masks by 3M for PhD.

The remaining authors declare that they have no competing interests and have no non-financial interests that may be relevant to the submitted work."

ACKNOWLEDGEMENTS

Thanks to the staff at the Beijing Centre for Disease Control and hospitals staff. We also acknowledge the support of patients and their families. This study was supported by UNSW Goldstar award.

CONTRIBUTORSHIP STATEMENT

CRM: lead investigator, responsible for conception and design of the study, analysing data and writing the manuscript; Yi Zhang: YZ: implementation and database management, AAC: statistical analysis and drafting of manuscript; HS, DZ, YC, HZ: recruitment and training, manuscript revision, Bayzidur Rahman: contributed to the statistical analysis and revision of manuscript, QW: implementation, contribution to design, analysis and drafting of paper.

TRANSPARENCY DECLARATION

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA SHARING STATEMENT

No additional data available

FIGURE LEGENDS

Figure1. Consort diagram of recruitment and follow-up

Figure 2: Survival curves for medical mask vs control arms

Figure 3: Survival curves for mask vs no mask group

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Table 1: Demographic and other characteristics of the index cases and household members

Variable	Mask arm (% and 95% CI)	Control arm (% and 95% CI)
Index case (number)	**123**	**122**
Gender (male)	56/123 45.5% (37.0% to 54.3)	45/122 36.9% (28.8% to 45.7%)
Age (mean)	40.2 (37.6 to 42.8)	39.7 (37.3 to 42.0)
Education (Under/postgraduate)	78/123 63.4% (54.6%-71.4%)	74/122 60.7% (51.8 to 68.9%)
Smoker (Current/Ex)	29/123 23.6% (16.9% to 31.8%)	26/122 21.3% (15.0% to 29.4%)
Pre-existing illness*	21/123 17.1% (16.2% to 31.0%)	16/122 13.1% (8.2% to 20.2%)
Influenza vaccination (Yes)	5/123 4.1% (1.7% to 9.2%)	5/122 4.1% (1.8% to 9.2%)
Household (members)	**302**	**295**
Number of house hold per arm	2.5	2.4
Gender (male)	149/302 49.0% (43.4% to 24.6%)	168/295 57.3% (51.6% to 62.9%)
Influenza vaccination (Yes) ‡	22/298 7.4% (4.9% to 10.9%)	30/285 10.5% (7.1% to 14.6%)
Age (mean)	38.3 (36.0 to 40.5)	36.4 (34.1 to 38.8)

* *Includes asthma, chronic obstructive pulmonary disease, diabetes, ischemic heart disease, immune-compromised and others*

† *Variable was created by taking average hours over the trial period.*

‡ *Missing data for 14 cases.*

Table 2: Number and proportion of household members reporting primary outcomes, by randomization arm and intention-to-treat analysis (n=597)*

	Clinical respiratory illness (CRI) No (rate person-days)	RR (95% CI)	Influenza like illness (ILI) No (rate person-days)		Laboratory confirmed viruses No (rate person-days)	RR (95% CI)
Mask arm**	4/2098 (1.91/1000)	0.65 (0.18-2.29)	1/2098 (0.48/1000)	0.32 (0.03-3.11)	1/2098 (0.48/1000)	0.97 (0.06-15.5)
Control arm***	6/2036 (2.95/1000)	Ref	3/2036 (1.47/1000)	Ref	1/2036 (0.49/1000)	Ref

* House hold members (mask arm 302 and control arm 295)
** Intracluster correlation coefficients is < 0.001
*** Intracluster correlation coefficients is < 0.001

Table 3: Hazard ratios from shared frailty Cox proportional hazards model for household members in masks vs. control arms (n=597)*

	Clinical respiratory illness (CRI) HR (95% CI)	Influenza like illness (ILI) HR (95% CI)	Laboratory confirmed viruses HR (95% CI)
Masks arm (Index case)	0.61 (0.18-2.13)	0.32 (0.03-3.13)	0.97 (0.06-15.54)
Control arm (Index case)	Ref	Ref	Ref
Age (Household)	1.03 (1.01-1.05)		

* House hold members (mask arm 302 and control arm 295)

Table 4: Number and proportion of participants reporting primary outcomes, by masks vs. no-mask groups (n=597)*

	Clinical respiratory illness (CRI) No (rate person-days)	*RR*	**Influenza like illness (ILI) No (rate person-days)**	*RR*	**Laboratory confirmed viruses No (rate person-days)**	*HR*†
Mask group	3/2694 (1.11/1000)	0.23 (0.06-0.88)	1/2694 (0.37/1000)	0.18 (0.02-1.71)	0/2694 (0/1000)	0.11 (0.01-4.40)
No mask group	7/1440 (4.86/1000)	Ref	3/1440 (2.08/1000)	Ref	2/1440 (0.70/1000)	Ref

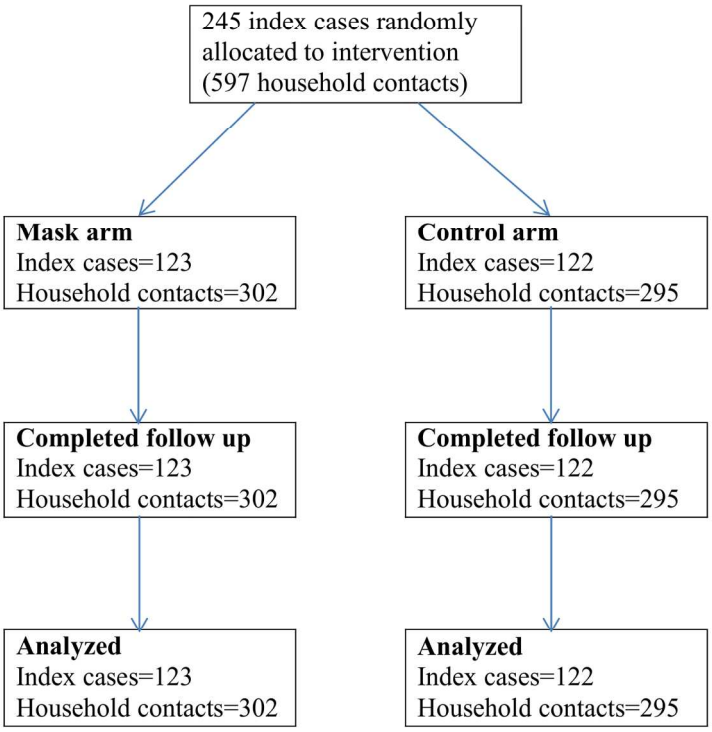
* Household members (mask group 387 and no-mask group 210)

† Calculated through Cox PH methods

Table 5: Hazard ratios from Shared frailty Cox proportional hazards model for masks vs. no masks groups (no randomisation) (n=597)*

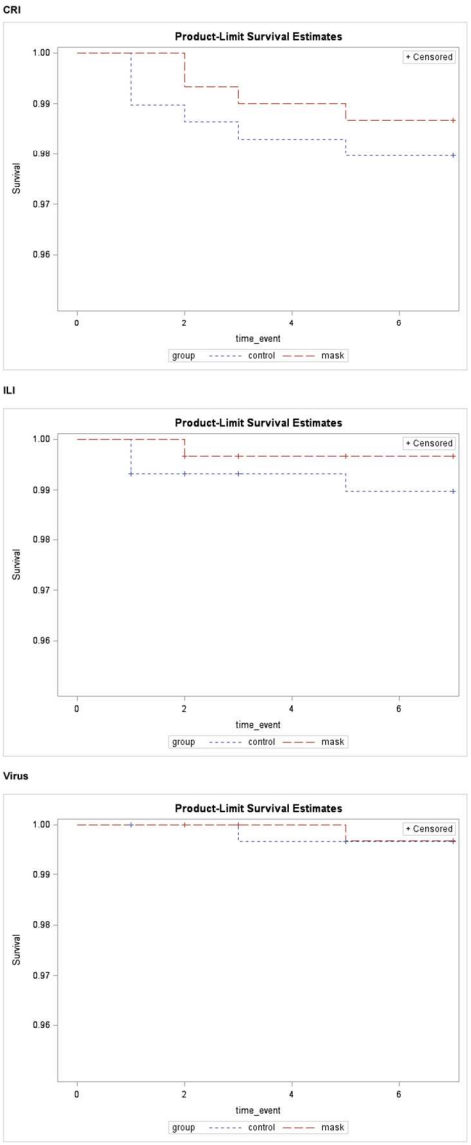
	Clinical respiratory illness (CRI) HR (95% CI)	**Influenza like illness (ILI) HR (95% CI)**	**Laboratory confirmed viruses HR (95% CI)**
Masks group (Index case)	**0.22 (0.06-0.86)**	0.18 (0.02 – 1.73)	0.11 (0.01 – 4.40)
No mask group (Index case)	Ref	Ref	Ref
Age (Household)	1.03 (1.00-1.06)		

* Household members (mask group 387 and no-mask group 210)



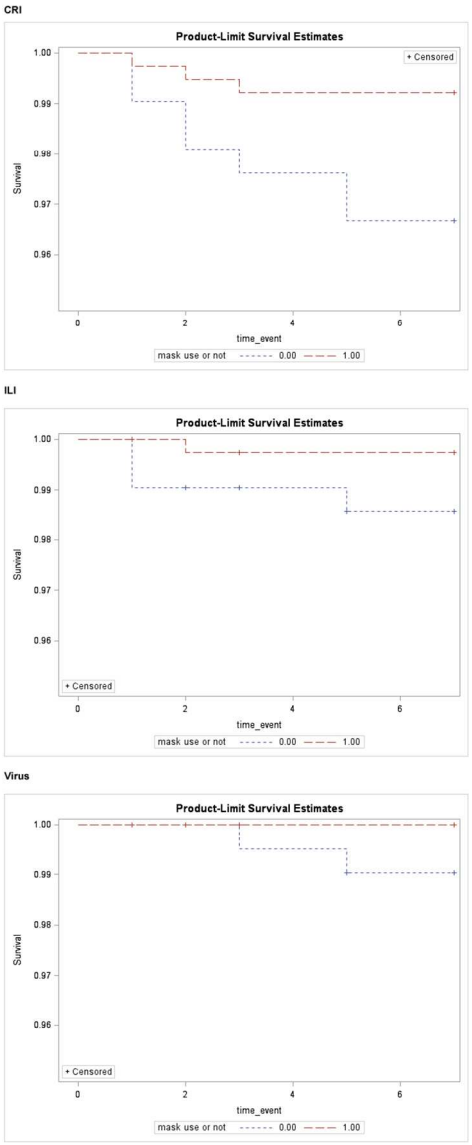
Consort diagram of recruitment and follow-up

160x160mm (300 x 300 DPI)



Survival curves for medical mask vs control arms

65x140mm (300 x 300 DPI)



Survival curves for mask vs no mask group

65x140mm (300 x 300 DPI)

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[1,2]	See table 2	2-3
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	5-6
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	6
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		**NA**
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	7
	4b	Settings and locations where the data were collected		**7**
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and	Whether outcome measures pertain to the cluster level, the individual participant level or both	7

		when they were assessed		
	6b	Any changes to trial outcomes after the trial commenced, with reasons		**Yes. Laboratory-confirmed bacterial colonization was an outcome in the protocols however we did could not test due to a lack of funding.**
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	11
	7b	When applicable, explanation of any interim analyses and stopping guidelines		**NA**
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		**7**
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	NA
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	

	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	7
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	7-8
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		**NA**
	11b	If relevant, description of the similarity of interventions		**NA**
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		**12**
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	12 and Figure 1
	13b	For each group, losses and exclusions after randomisation, together with	For each group, losses and exclusions for both clusters and	13

		reasons	individual cluster members	
Recruitment	14a	Dates defining the periods of recruitment and follow-up		**6**
	14b	Why the trial ended or was stopped		**6**
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	Table1 and table 2
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	Table 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		**Table 2**
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		**Table 4 and table 5**
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[3])		**NA**
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		**17-18**
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	17-18

Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	**15-17**
Other information			
Registration	23	Registration number and name of trial registry	**4**
Protocol	24	Where the full trial protocol can be accessed, if available	**4**
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	**4**

** Note: page numbers optional depending on journal requirements*

Table 2: Extension of CONSORT for abstracts[1,2] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	**Identification of study as cluster randomised**
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	**Eligibility criteria for clusters**
Interventions	Interventions intended for each group	
Objective	Specific objective or hypothesis	**Whether objective or hypothesis pertains to the cluster level, the individual participant level or both**
Outcome	Clearly defined primary outcome for this report	**Whether the primary outcome pertains to the cluster level, the individual participant level or both**
Randomization	How participants were allocated to interventions	**How clusters were allocated to interventions**
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	
Results		
Numbers randomized	Number of participants randomized to each group	**Number of clusters randomized to each group**
Recruitment	Trial status[1]	
Numbers analysed	Number of participants analysed in each group	**Number of clusters analysed in each group**
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	**Results at the cluster or individual participant level as applicable for each primary outcome**
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	
Trial registration	Registration number and name of trial register	
Funding	Source of funding	

[1] Relevant to Conference Abstracts

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BMJ Open

Cluster randomised controlled trial to examine medical mask use as source control for people with respiratory illness

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-012330.R2
Article Type:	Research
Date Submitted by the Author:	12-Oct-2016
Complete List of Authors:	MacIntyre, Raina; University of New South Wales, Zhang, Yi; Institute for Infectious Disease and Endemic Disease Control, Beijing Center forDisease Prevention and Control (CDC) Chughtai, Abrar; Univesity of New South Wales, School of Public Health and Community Medicine Seale, Holly; University of New South Wales, School of Public Health and Community Medicine Zhang, Daitao; Institute for Infectious Disease and Endemic Disease Control, Beijing Center forDisease Prevention and Control (CDC) Chu, Yanhui; Xicheng District Center for Diseases Prevention and Control, Beijing , China Zhang, Haiyan ; Dongcheng District Center for Diseases Prevention and Control, Beijing, China Rahman, Bayzidur; University of New South Wales, School of Public Health and Community Medicine Wang, Quanyi; Institute for Infectious Disease and Endemic Disease Control, Beijing Center for disease prevention and control
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Infectious diseases
Keywords:	Mask, Influenza, Infection control < INFECTIOUS DISEASES

Cluster randomised controlled trial to examine medical mask use as source control for people with respiratory illness

Chandini Raina MacIntyre, Yi Zhang, Abrar Ahmad Chughtai, Holly Seale, Daitao Zhang, Yanhui Chu, Haiyan Zhang, Bayzidur Rahman, Quanyi Wang

School of Public Health and Community Medicine UNSW Medicine University of New South Wales Sydney Australia and College of Public Service & Community Solutions, Arizona State University, Phoenix, Arizona, United States, The Beijing Centre for Disease Prevention and Control Beijing China, XiCheng district CDC Beijing China, Dongcheng district CDC Beijing China, Chandini Raina MacIntyre Professor and Head of School of Public Health and Community Medicine University of New South Wales, Yi Zhang Doctor The Beijing Centre for Disease Prevention and Control, Abrar Ahmad Chughtai Post doctorate Research Fellow University of New South Wales, Holly Seale Associate Lecturer University of New South Wales, Daitao Zhang, Doctor The Beijing Centre for Disease Prevention and Control, Yanhui Chu Doctor Xicheng District Center for Diseases Prevention and Control, Haiyan Zhang Doctor Dongcheng District Center for Diseases Prevention and Control, Bayzidur Rahman, Senior Lecturer University of New South Wales, Quanyi Wang Professor The Beijing Centre for Disease Prevention and Control

Corresponding author

Dr. Abrar Ahmad Chughtai

Level 2, Samuels Building, School of Public Health & Community Medicine, UNSW Medicine University of New South Wales, Sydney 2052, Australia

Telephone: +61 (2) 9385 3129 Fax: +61 (2) 9313 6185

Email: doctorahmad75@gmail.com

ABSTRACT

Rationale: Medical masks are commonly used by sick individual with influenza-like illness (ILI) to prevent spread of infections to others, but clinical efficacy data are absent.

Objective: Determine whether medical mask use by sick individuals with ILI protects well contacts from related respiratory infections.

Setting: Six major hospitals in two districts of Beijing, China

Design: Cluster randomised controlled trial

Participants: 245 index cases with ILI

Intervention: Index cases with ILI were randomly allocated to medical mask and control arms. A total of 43 index cases in the control arm also used a mask during the study period, an as-treated post-hoc analysis was performed by comparing outcomes among household members of index cases who used a mask (mask group) with household members of index cases who did not use a mask (no-mask group).

Main outcome measure: Primary outcomes measured in household members were clinical respiratory illness, ILI, and laboratory-confirmed viral respiratory infection.

Results:

In intention-to-treat analysis, rates of clinical respiratory illness (RR 0.61, 95% CI 0.18 to 2.13), ILI (RR 0.32, 95% CI 0.03 to 3.13) and laboratory-confirmed viral infections (RR 0.97, 95% CI 0.06 to 15.54) were consistently lower in the mask arm compared to control, although not statistically significant. A post-hoc comparison between the mask versus no-

mask groups showed a protective effect against clinical respiratory illness, but not against ILI and laboratory-confirmed viral respiratory infections.

Conclusion:

The study indicates a potential benefit of medical masks for source control, but was limited by small sample size and low secondary attack rates. Larger trials are needed to confirm efficacy of medical masks as source control.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths

1. We conducted a cluster randomised control trial to examine the efficacy of medical masks as source control .
2. The rates of all outcomes were consistently lower in the mask arm compared to control, although difference was not statistically significant by intention to treat analysis.
3. Comparison between the mask versus no-mask groups in post-hoc analysis showed a significantly protective effect against clinical respiratory illness, indicating a potential benefit of medical masks for source control.

Limitations

4. The sample size was small and the study was underpowered to detect a statistically significant difference in outcome in the intention-to-treat analysis.
5. Removal of masks in the intervention arm during meal times may have reduced efficacy and biased the results toward the null.

Trial registration: Australian New Zealand Clinical Trials Registry (ANZCTR), ACTRN12613000852752 (http://www.anzctr.org.au).

Funding source: This study was supported by UNSW Goldstar award.

INTRODUCTION

Medical masks are commonly used in healthcare settings for two main purposes: 1) by well healthcare workers (HCWs) to protect them from infections transmit by droplet route and splash and spray of blood and body fluids; and 2) by sick individuals to prevent transmission to others (source control) (1, 2). There are currently major gaps in our knowledge about the impact of masks on the transmission of respiratory infections (3). Most clinical trials have been focused on the protection of the well wearer, rather than on source control (3). Cloth and medical masks were originally developed as source control to prevent contamination of sterile sites by the wearer in operating theatres (OTs) (4, 5), however their effectiveness in preventing surgical site infections is yet to be proven (6-8).

Although masks are also widely used in the community to prevent spread of infection from sick and infectious people (9-13), the majority of data on their use are observational and derived from outbreaks and pandemics. Among the 9 randomized controlled trials (RCTs) in household and community settings to date (3), only one examined the role of masks as source control and was inconclusive (14). In other clinical trials, masks were either used by both sick patients (index cases as source control) and their household members (15-17) or used only by household members (18-20). Most of these studies failed to show any efficacy of mask use in preventing spread of infections from the sick individuals.

Masks are also used to prevent surgical site infections in the operating theatre (OT) (3), although most studies failed to show any efficacy against this indication (6-8, 21). Only one clinical trial reported high infection rates after surgery if masks were not used by the surgeon in the OT (22). Among the five clinical trials in the healthcare setting to test the efficacy of masks/ respirators as respiratory protection (3), none examined the use of masks

as source control. Laboratory studies generally support the use of medical masks to prevent spread of infections from influenza and TB patients to their contacts (23-25).

Mask use as source control in healthcare settings has now been included in standard infection control precautions during periods of increased respiratory infection activity in the community, yet there is no clinical efficacy evidence to support this recommendation. The aim of this study was to determine whether medical mask use by people in a community setting with influenza-like illness (ILI) protects well contacts from infection.

METHODS

Design

An RCT was conducted in fever clinics in six major hospitals in two districts of Beijing, China. The fever clinics are outpatient departments for the assessment and treatment of febrile patients.. The recruitment of participants started on 18th November 2013 and completed on 20 January 2014. Adults who attended the fever clinic were screened by hospital staff to identify if they were eligible for the study. A study staff member approached eligible patients when they presented in the clinic and invited them to participate in the study. Recruited patients meeting the case definition of ILI (see below) were referred to as index cases, which is the first case in a potential chain of infection transmission.

Eligibility

Patients 18 years and older (index cases) with ILI (defined as fever ≥38ºC plus one respiratory symptom including cough, nasal congestion, runny nose, sore throat or sneezes) who attended a fever outpatient clinic during the study period, had no history of ILI amongst

household members in the prior 14 days and who lived with at least two other people at home were recruited for the study. ILI was used as a selection criterion to achieve high specificity for index cases. Patients who were unable or refused to give consent, had onset of symptoms >24 hours prior to recruitment, were admitted to hospital, resided in a household with less than two other people, or have other ill household members at home were excluded from the study.

Randomisation

After providing informed consent, 245 index cases were included and randomly allocated to intervention (mask) and control (no mask) arms. A research team member (YZ) did the random allocation sequence using Microsoft Excel and doctors enrolled the participants randomly to intervention and control arms. Patients had an equal chance to be in the either intervention or control arm. One hundred and twenty three index cases and 302 household contacts were included in the mask (source control) arm and 122 index cases and 295 household contacts were included in control arm (Figure 1). Cases and their household contacts were assigned together as a cluster to either intervention or control arm.

Intervention

The mask or no mask intervention was applied to the index cases and respiratory illness was measured in household contacts. Index cases (patients with ILI) in the intervention arm wore a medical mask at home. Index cases were asked to wear a mask (3M 1817 surgical mask) whenever they were in the same room as a household member or a visitor to the household. They were allowed to remove their masks during meal times and while asleep. Index cases were shown how to wear the mask and instructed to wash their hands when donning and

doffing the mask. Index cases were provided with three masks per day for 7 days (21 masks in total). They were informed that they could cease wearing a mask once their symptoms resolved. Index cases in the control arm did not receive any intervention. Mask use by other household members was not required and not reported.

Outcome measures

Respiratory illness outcomes were measured in household contacts of the index cases. Primary endpoints measured in household contacts included: (1) clinical respiratory illness (CRI), defined as two or more respiratory symptoms (cough, nasal congestion, runny nose, sore throat or sneezes) or one respiratory symptom and a systemic symptom (chill, lethargy, loss of appetite, abdominal pain, muscle or joint aches) ; (2) ILI, defined as fever ≥38ºC plus one respiratory symptom ; and (3) laboratory-confirmed viral respiratory infection, defined as detection of adenoviruses, human metapneumovirus, coronaviruses 229E/NL63 and OC43/HKU1, parainfluenzaviruses 1, 2 and 3, influenza viruses A and B, respiratory syncytial virus A and B, or rhinovirus A/B by nucleic acid testing (NAT) using a commercial multiplex polymerase chain reaction (PCR) (Seegen, Inc., Seoul, Korea) (26-28).

If any respiratory or systemic symptoms occurred in household members, index cases were instructed to notify the study coordinator. Symptomatic household members were asked to complete "sick follow-up" questionnaires and anyone who met the CRI definition was tested for laboratory-confirmed viral respiratory infections.

Data collection and follow-up

At baseline detailed clinical and demographic information including household structure was collected from index cases and their household members. This included age, sex, smoking

history, comorbidities, medications, hand washing practices, influenza vaccination and normal practices around the use of masks.

Follow-up period (7 days): Each index case was asked to keep a diary to record activities, symptoms and daily temperatures for seven days. Symptoms in the household members were also recorded in the diary cards and index cases were asked to report any symptom. The index cases were asked to contact the study coordinator if any of the following symptoms appeared in household members: cough, nasal congestion, runny nose, sore throat, sneezes, chill, lethargy, loss of appetite, abdominal pain and muscle or joint aches. The study coordinator then assessed the household member and completed a follow-up survey. Samples were obtained from all symptomatic cases. All index cases in the intervention and control arms were also asked to document compliance with mask use (27, 28). Diary cards to record mask use were given to each index case, and they were asked to carry them during the day. Diary cards were returned to the investigators at the end of the study. The study coordinator also contacted index cases via telephone on every alternate day to check whether any household member developed symptoms. Assessors were not blinded, because the intervention (mask wearing) is visible. However, laboratory testing was blinded.

Sample Collection and Laboratory Testing

Samples were collected from index patients at the time of recruitment and from symptomatic household members during follow-up. Household members were provided with an information sheet and written consent was sought before sampling. Only those household members who provided consent were swabbed. If the sick household member

was aged <18years, consent was obtained from a parent or guardian. Swabs were taken at the home by trained investigators.

Double rayon-tipped, plastic-shafted swabs were used to swab both tonsilar areas and the posterior pharyngeal wall of symptomatic subjects. The swabs were then transported immediately after collection to the Beijing CDC laboratories, or stored at 4ºC within 48 hrs if transport was delayed.

Viral DNA/RNA was extracted from each respiratory specimen using the Viral Gene-spin TM Kit (iNtRON Biotechnology, Inc., Seoul, Korea) according to the manufacturer's instructions. Reverse transcription was performed using the RevertAidTM First Strand cDNA Synthesis Kit (Fermentas, ON, Canada) to synthesize cDNA. Multiplex PCR was carried out using the Seeplex® RV12 Detection Kit (Seegen, Inc., Seoul, Korea) to detect adenoviruses, human metapneumovirus, coronavirus 229E/NL63 and OC43/HKU1, parainfluenzaviruses 1, 2 or 3, influenza viruses A or B, respiratory syncytial virus A or B, and rhinovirus A/B. A mixture of 12 viral clones were used as a positive control template, and sterile deionized water was used as a negative control. Viral isolation by MDCK cell culture was undertaken for some of the influenza samples that were NAT positive. Specimen processing, DNA/RNA extraction, PCR amplification, and PCR product analyses was conducted in different rooms to avoid cross-contamination.

Sample size

In this cluster randomized design, the household was the unit of randomization and the average household size was three people. Assuming the attack rate of CRI in the control households was 16-20% (based on the results of a previously published household mask

trial) (18), with 5% significance level and 85% power, minimum relative risk of 0.5 (intervention/control), 385 participants were required in each arm, which was composed of 118 households and on average, three members per household. In this calculation, we assumed that the intracluster correlation coefficient (ICC) was 0.1. An estimated 250 patients with ILI were recruited into the study to allow for possible index case dropout during the study.

Data analysis

Descriptive statistics were compared in mask and control arms and respiratory virus infection attack rates were quantified. Data from the diary cards were used to calculate person-days of infection incidence. Primary endpoints were analysed by intention to treat across the study arms and ICC for clustering by household was estimated using clchi2 command in Stata (29). Relative risks were calculated for the mask arm. Kaplan-Meier survival curves were generated to compare the survival pattern of outcomes across mask and control arms. Differences between the survival curves were assessed through Log-rank test. The analyses were conducted in individual level and hazard ratios (HR) were calculated using Cox proportional hazards model after adjusting for clustering by household by adding a shared frailty to the model. Due to very few outcome events encountered a multivariable Cox model was not appropriate. We checked the effect of individual potential confounders on the outcome variable fitting univariable Cox models. Because there were 10 cases of CRI, we included this variable in a multivariable cluster adjusted Cox model. Multivariate analyses were not performed for ILI and laboratory-confirmed viruses because of low numbers.

A total of 43 index cases in the control arm also used a mask during the study period (at least one hour per day) and 7 index cases in the masks arm did not use a mask at all, so a post-hoc sensitivity analysis was carried out to compare outcomes among household members of index cases who used a mask (hereafter "mask group"), with those of index cases who did not use a mask (hereafter "no-mask group"). All statistical analyses were conducted using Stata version 13 (30).

Ethics approval

Ethics approval was obtained from the Beijing Center for Disease Prevention and Control IRB and the Human Research Ethics Committee of the University of New South Wales (UNSW), Australia (HREC approval number HC13236).

RESULTS

A total of 245 index patients were randomised into the mask arm (n=123) or the control arm (n=122). The mask arm had on average 2.5 household contacts per index case (n=302), while the control arm had 2.4 household contacts per index cases (n=295). Characteristics of index cases and household members are presented in table 1. There was no significant difference between arms, and most characteristics, including medication use (data not shown), were generally similar. Viruses were isolated from 60% (146/245) index cases. Influenza was the most common virus isolated from 115 (47%) cases - Influenza A - 100, Influenza B - 11 and Influenza A&B - 4. Other viruses isolated from index cases were, rhinovirus (14), NL63 (12) and C229E (7). More than one virus was isolated in 48 (20%) index cases, including 17 coinfections with influenza.

Table 2 shows the intention to treat analysis. CRI was reported in 4 (1.91/1000 person-days) household members in the mask arm, compared to 6 household members (2.95/1000 person-days) in the control arm (RR 0.65, 95% CI 0.18 to 2.29). Only 1 case (0.48/1000 person-days) of ILI was reported in the mask arm, compared to 3 cases (1.47/1000 person-days) in the control arm (RR 0.32, 95% CI 0.03 to 3.11). Two laboratory confirmed infections were identified among symptomatic household members from separate household. One household member had the same infection (influenza H1N1) as the respective index case. Rhinovirus was isolated from other household member. However no pathogen was isolated from respective index case. The two cases of laboratory-confirmed viral respiratory infections of household members occurred in separate study arms (RR 0.97, 95% CI 0.06 to 15.5). The Kaplan-Meier curves showed no significant differences in the outcomes between two arms (P-value > 0.050) (Figure 2).

Duration of contact of index cases with household members was 10.4 hours and 11.1 hours in mask and control arms respectively. On average, participants in the mask arm used a mask for 4.4 hours, while participants in the control arm used a mask for 1.4 hours. In a univariable Cox model only the age of household contact was significantly associated with the CRI (Table 3). There was no association between mask use by the index cases and rates of infectious outcomes in household members (Table 3). Although the risks of CRI (RR 0.61, 95% CI 0.18 to 2.13), ILI (RR 0.32, 95% CI 0.03 to 3.13) and laboratory-confirmed viral infections (RR 0.97, 95% CI 0.06 to 15.54) were lower in the mask arm, the difference was not statistically significant.

Tables 4 & 5 show a sensitivity analysis comparing outcomes among household members of index cases using a mask (“mask group”), with those of index cases who did not use a mask

("no-mask group"). Overall, 159 index cases (65%) used a mask during the trial period including 43 subjects from the control arm. Three hundred and eighty seven household members were included in the mask group and 210 were included in the no-mask group. Rates of all outcomes were lower in the mask group, and CRI was significantly lower in the contacts of the mask group compared to the contacts of the no-mask group. The Kaplan-Meier curves (Figure 3) showed a significant difference in the rate of CRI among the mask and no-mask groups (P- 0.020).

After adjusting for the age of household contacts, the risk of CRI was 78% lower in the contacts of the mask group (RR 0.22, 95% CI 0.06 to 0.86), compared to contacts of the no-mask group. Although the risks of ILI (RR 0.18, 95% CI 0.02 to 1.73) and laboratory-confirmed viral respiratory infections (RR 0.11, 95% CI 0.01 to 4.40) were also lower in the mask group, the difference was not statistically significant.

DISCUSSION

Masks are commonly recommended as source control for patients with respiratory infections to prevent the spread of infection to others (2, 3), but data on the clinical efficacy of this approach are sparse. We did not find a significant benefit of medical masks as source control, but rates of CRI and ILI in household members were consistently lower in the mask arm compared to the control arm. The study was underpowered to detect a statistically significant difference. The additional analysis by actual mask use showed significantly lower rates of CRI in mask group compared to the no-mask group, suggesting larger trials should be conducted to further examine the efficacy of masks as source control.

Our findings are consistent with previous research in community and household settings, where the efficacy of masks as source control was measured. To date, only one RCT has been conducted in the community setting to examine the role of masks in preventing spread of infection from wearers (3). Canini et al. conducted an RCT in France during the 2008–2009 influenza season and randomised index patients into medical mask (52 households and 148 contacts) and control arms (53 households and 158 contacts). ILL was reported in 16.2% and 15.8% contacts in the intervention and control arms, respectively, and the difference was not statistically significant (mean difference 0.40%, 95%CI: -10% to 11%, P= 1.00). The trial was concluded early due to low recruitment and the subsequent influenza A (H1N1)pdm09 pandemic (14). In addition, masks were also used by both index cases and household members in some community based RCTs with mixed interventions (15, 16). Cowling et al. conducted two RCTs in Hong Kong to examine the efficacy of masks, and index cases were randomised into medical mask, medical mask plus hand hygiene, hand hygiene and control arms. Both index cases and household members used masks. The rates of laboratory-confirmed influenza and ILI were the same in the intervention and control groups in the intention to treat analysis (15). However, in the second trial mask use with hand hygiene was protective in household contacts when the intervention was applied within 36 hours of onset of symptoms in the index case (OR 0.33, 95% CI, 0.13 to 0.87) (16). As masks were used by both sick patients and their household members in these studies, the effect of mask being “source control” is more difficult to precisely quantify.

Masks are not designed for respiratory protection and are commonly used in the healthcare setting to prevent spread of infections from the wearer, whether worn by a sick patient or well staff member (1, 3). One such use is the wearing of masks by well surgeons and other

OT staff to protect patients from contamination during surgery. Presumably, the exhaled pathogen load would be much higher in a sick patient compared to a well surgeon, and therefore the use of a mask for source control in sick patients may have more benefit than OT use of source control.

This study has some limitations. The sample size was small and the study may have been underpowered to detect a statistically significant difference in outcome in the intention-to-treat analysis. Post-hoc analysis however, showed a potential benefit of medical masks for source control. It is possible that infection transmission may have occurred during meal times (when patients were not required to wear a mask). This would have the effect of biasing the results toward the null. In the sample size calculations, we assumed 16-20% attack rate of CRI in the control arm, based on the results of a previously published household mask trial (18). However the secondary attack rates were much lower in this study which might be due to testing only symptomatic cases.

In a univariable Cox model only the age of household contact was significantly associated with the CRI. All other variables were uniformly distributed among the study arms so we only adjusted for age of household contact in the analysis of CRI as an outcome. Multivariate analyses were not performed for ILI and laboratory-confirmed viruses. However some variables may have impact on the number of events. For example the rates of hand hygiene were higher among the "control" arm compared to the mask arm (109/122, 89.3% vs. 98/123, 79.7%) which may have had an impact on the number of outcome events. Due to low event rates and non-significant difference of hand hygiene among the two arms, we did not adjust for hand hygiene in any analysis. Further, inclusion of hand hygiene in the model did not change the HR. Finally, post-hoc analyses are potentially biased due to loss of

randomisation and it was added as a sensitivity analysis in this study because of deviations from protocol in mask wearing.

Despite a lack of evidence, most health organisations and countries recommend the use of masks by sick patients as source control (1, 2). Masks are used commonly by TB patients, although clinical trials have not been conducted for this indication. There is a need to conduct larger trials to confirm the suggestion of benefit in our study. If source control is effective in reducing hospital transmission of infection, this may have a practical benefit to mitigate the problem of poor compliance with mask wearing among well HCWs (3). Compliance with any intervention for someone who is well and asymptomatic is far more challenging than compliance in people who are unwell (31), so source control may have an important role in hospital infection control. Reducing the transmission of respiratory pathogens by source patients could also have further benefits in the community in preventing transmission of infection to close contacts such as those in the same household, and should be studied further.

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COMPETING INTERESTS

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare that;

1. Professor C. Raina MacIntyre: Raina MacIntyre has held an Australian Research Council Linkage Grant with 3M as the industry partner, for investigator driven research. 3M have also contributed supplies of masks and respirators for investigator-driven clinical trials. She has received research grants and laboratory testing as in-kind support from Pfizer, GSK and Bio-CSL for investigator-driven research.
2. Dr Holly Seale had a NHMRC Australian based Public Health Training Fellowship at the time of the study (1012631). She has also received funding from vaccine manufacturers GSK, bio-CSL and Saniofi Pasteur for investigator-driven research and presentations.
3. Dr. Abrar Chughtai had testing of filtration of masks by 3M for PhD.

The remaining authors declare that they have no competing interests and have no non-financial interests that may be relevant to the submitted work."

ACKNOWLEDGEMENTS

Thanks to the staff at the Beijing Centre for Disease Control and hospitals staff. We also acknowledge the support of patients and their families. This study was supported by UNSW Goldstar award.

CONTRIBUTORSHIP STATEMENT

CRM: lead investigator, responsible for conception and design of the study, analysing data and writing the manuscript; Yi Zhang: YZ: implementation and database management, AAC: statistical analysis and drafting of manuscript; HS, DZ, YC, HZ: recruitment and training, manuscript revision, Bayzidur Rahman: contributed to the statistical analysis and revision of manuscript, QW: implementation, contribution to design, analysis and drafting of paper.

TRANSPARENCY DECLARATION

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA SHARING STATEMENT

No additional data available

FIGURE LEGENDS

Figure1. Consort diagram of recruitment and follow-up

Figure 2: Survival curves for medical mask vs control arms (2a) CRI, (2b) ILI, (2c) laboratory-confirmed viral respiratory infections

Figure 3: Survival curves for mask vs no mask group (3a) CRI, (3b) ILI, (3c) laboratory-confirmed viral respiratory infections

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Table 1: Demographic and other characteristics of the index cases and household members

Variable	Mask arm (% and 95% CI)	Control arm (% and 95% CI)
Index case (number)	**123**	**122**
Gender (male)	56/123 45.5% (37.0% to 54.3)	45/122 36.9% (28.8% to 45.7%)
Age (mean)	40.2 (37.6 to 42.8)	39.7 (37.3 to 42.0)
Education (Under/postgraduate)	78/123 63.4% (54.6%-71.4%)	74/122 60.7% (51.8 to 68.9%)
Smoker (Current/Ex)	29/123 23.6% (16.9% to 31.8%)	26/122 21.3% (15.0% to 29.4%)
Pre-existing illness*	21/123 17.1% (16.2% to 31.0%)	16/122 13.1% (8.2% to 20.2%)
Influenza vaccination (Yes)	5/123 4.1% (1.7% to 9.2%)	5/122 4.1% (1.8% to 9.2%)
Household (members)	**302**	**295**
Number of house hold per arm	2.5	2.4
Gender (male)	149/302 49.3% (43.4% to 24.6%)	168/295 56.9% (51.6% to 62.9%)
Influenza vaccination (Yes) ‡	22/298 7.4% (4.9% to 10.9%)	30/285 10.5% (7.1% to 14.6%)
Age (mean)	38.3 (36.0 to 40.5)	36.4 (34.1 to 38.8)

*. *Includes asthma, chronic obstructive pulmonary disease, diabetes, ischemic heart disease, immune-compromised and others*

† *Variable was created by taking average hours over the trial period.*

‡ *Missing data for 14 cases.*

Table 2: Number and proportion of household members reporting primary outcomes, by randomization arm and intention-to-treat analysis (n=597)*

	Clinical respiratory illness (CRI) No (rate person-days)	RR (95% CI)	Influenza-like illness (ILI) No (rate person-days)		Laboratory-confirmed viral respiratory infections No (rate person-days)	RR (95% CI)
Mask arm**	4/2098 (1.91/1000)	0.65 (0.18-2.29)	1/2098 (0.48/1000)	0.32 (0.03-3.11)	1/2098 (0.48/1000)	0.97 (0.06-15.5)
Control arm***	6/2036 (2.95/1000)	Ref	3/2036 (1.47/1000)	Ref	1/2036 (0.49/1000)	Ref

* House hold members (mask arm 302 and control arm 295)

** Intracluster correlation coefficients is < 0.001

*** Intracluster correlation coefficients is < 0.001

Table 3: Hazard ratios from shared frailty Cox proportional hazards model for household members in masks vs. control arms (n=597)*

	Clinical respiratory illness (CRI) HR (95% CI)**	Influenza-like illness (ILI) HR (95% CI)**	Laboratory-confirmed viral respiratory infections HR (95% CI)**
Masks arm (Index case)	0.61 (0.18-2.13)	0.32 (0.03-3.13)	0.97 (0.06-15.54)
Control arm (Index case)	Ref	Ref	Ref
Age (Household)	1.03 (1.01-1.05)		

* House hold members (mask arm 302 and control arm 295)

** Multivariate analysis was performed as there were 10 cases of CRI and age was also significant in the univariate analysis. Multivariate analyses were not performed for ILI and laboratory-confirmed viral respiratory infections due to low number of cases.

Table 4: Number and proportion of participants reporting primary outcomes, by masks vs. no-mask groups (n=597)*

	Clinical respiratory illness (CRI) No (rate person-days)	*RR*	**Influenza-like illness (ILI) No (rate person-days)**	*RR*	**Laboratory-confirmed viral respiratory infections No (rate person-days)**	*HR*†
Mask group	3/2694 (1.11/1000)	0.23 (0.06-0.88)	1/2694 (0.37/1000)	0.18 (0.02-1.71)	0/2694 (0/1000)	0.11 (0.01-4.40)
No mask group	7/1440 (4.86/1000)	Ref	3/1440 (2.08/1000)	Ref	2/1440 (0.70/1000)	Ref

* Household members (mask group 387 and no-mask group 210)

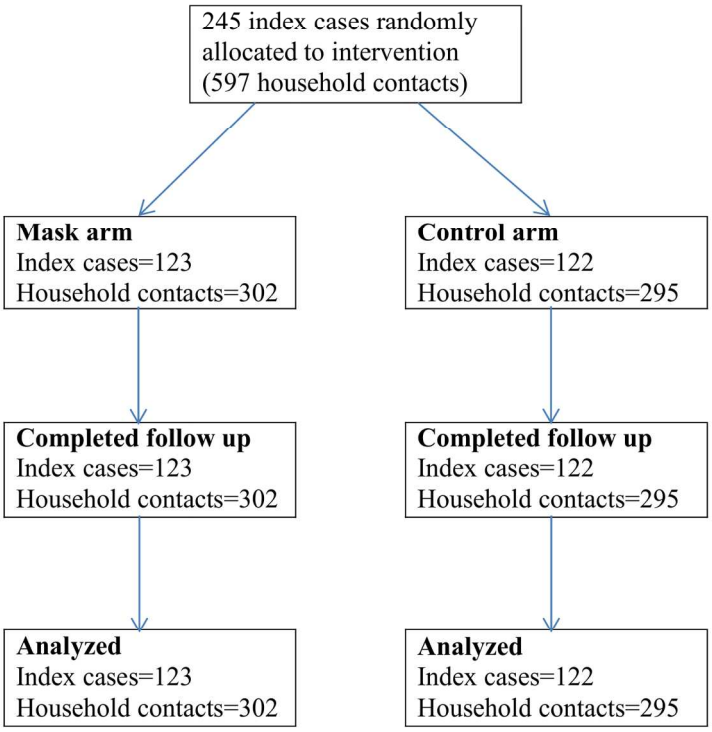
† Calculated through Cox PH methods

Table 5: Hazard ratios from Shared frailty Cox proportional hazards model for masks vs. no masks groups (no randomisation) (n=597)*

	Clinical respiratory illness (CRI) HR (95% CI)**	**Influenza-like illness (ILI) HR (95% CI)****	**Laboratory-confirmed viral respiratory infections HR (95% CI)****
Masks group (Index case)	**0.22 (0.06-0.86)**	0.18 (0.02 – 1.73)	0.11 (0.01 – 4.40)
No mask group (Index case)	Ref	Ref	Ref
Age (Household)	1.03 (1.00-1.06)		

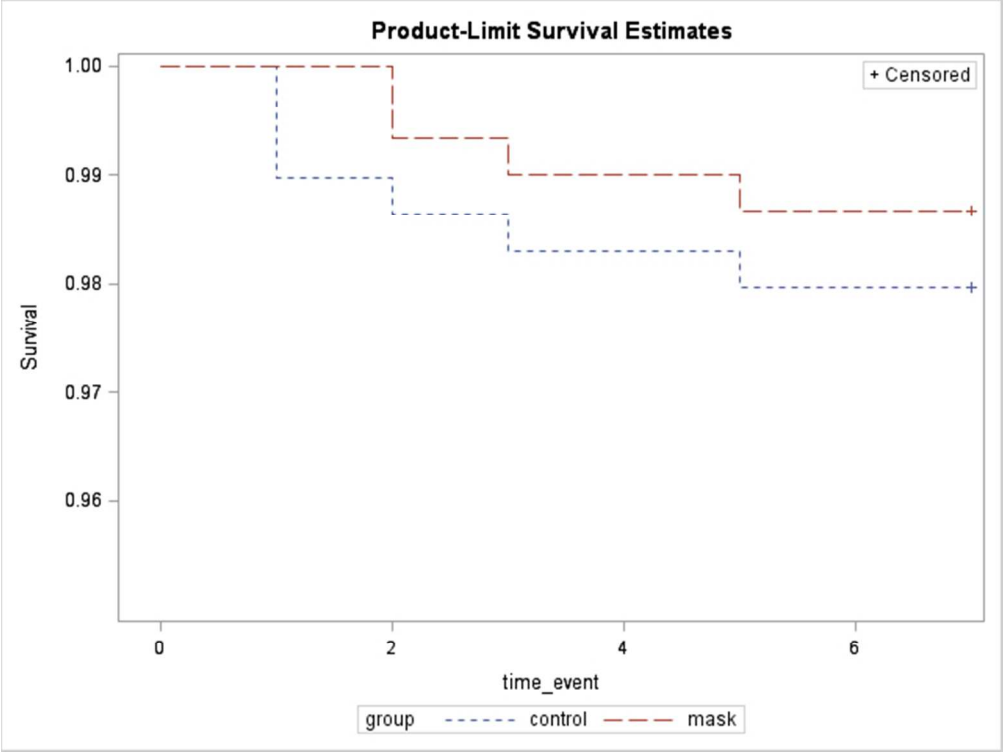
* Household members (mask group 387 and no-mask group 210)

** Multivariate analysis was performed as there were 10 cases of CRI and age was also significant in the univariate analysis. Multivariate analyses were not performed for ILI and laboratory-confirmed viral respiratory infections due to low number of cases

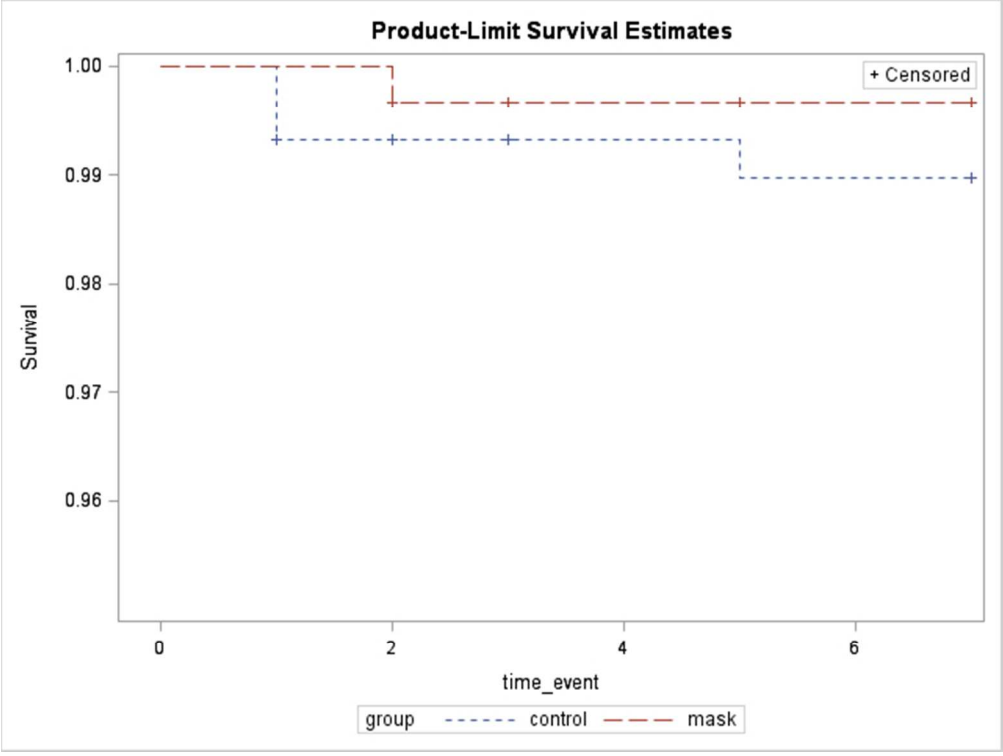


Consort diagram of recruitment and follow-up

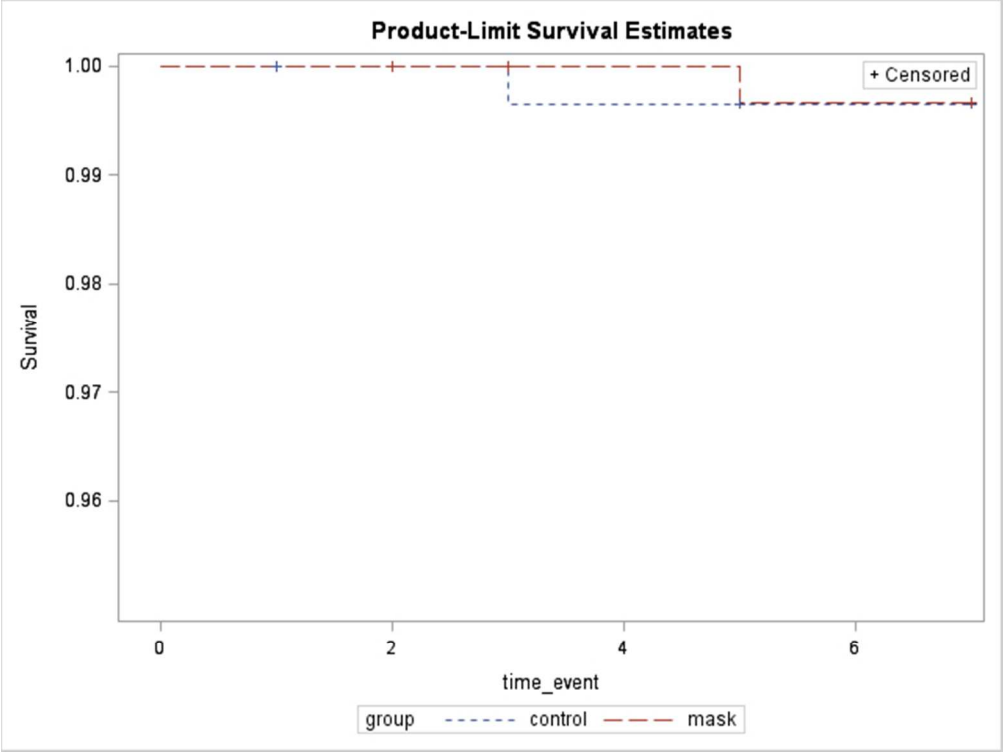
160x160mm (300 x 300 DPI)



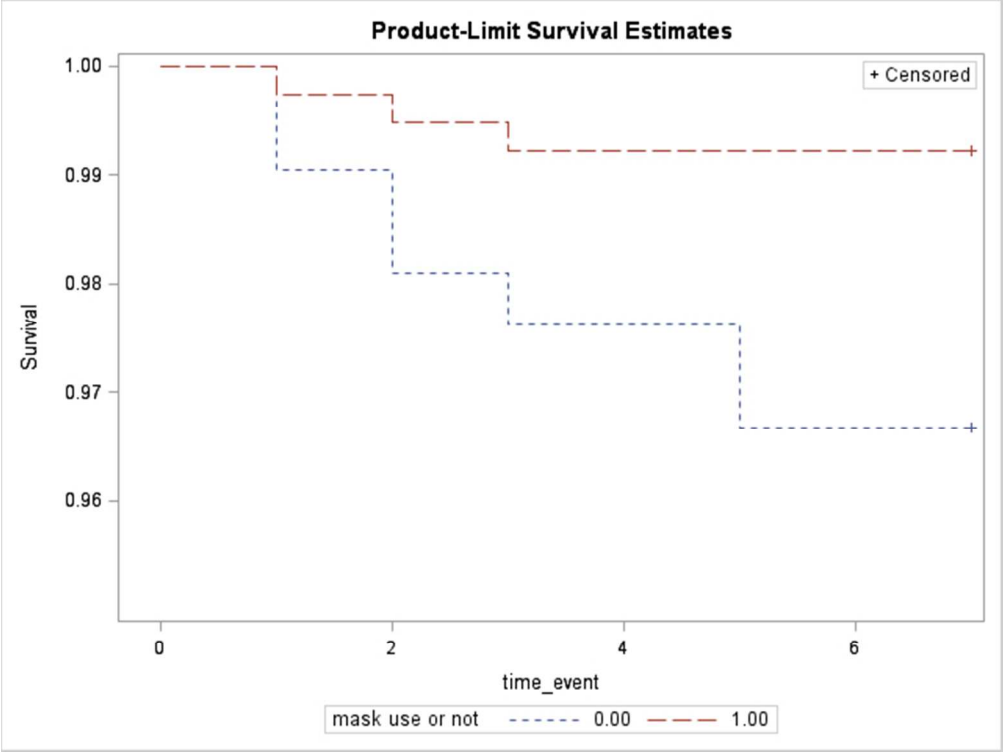
Survival curves for medical mask vs control arms (2a) CRI,



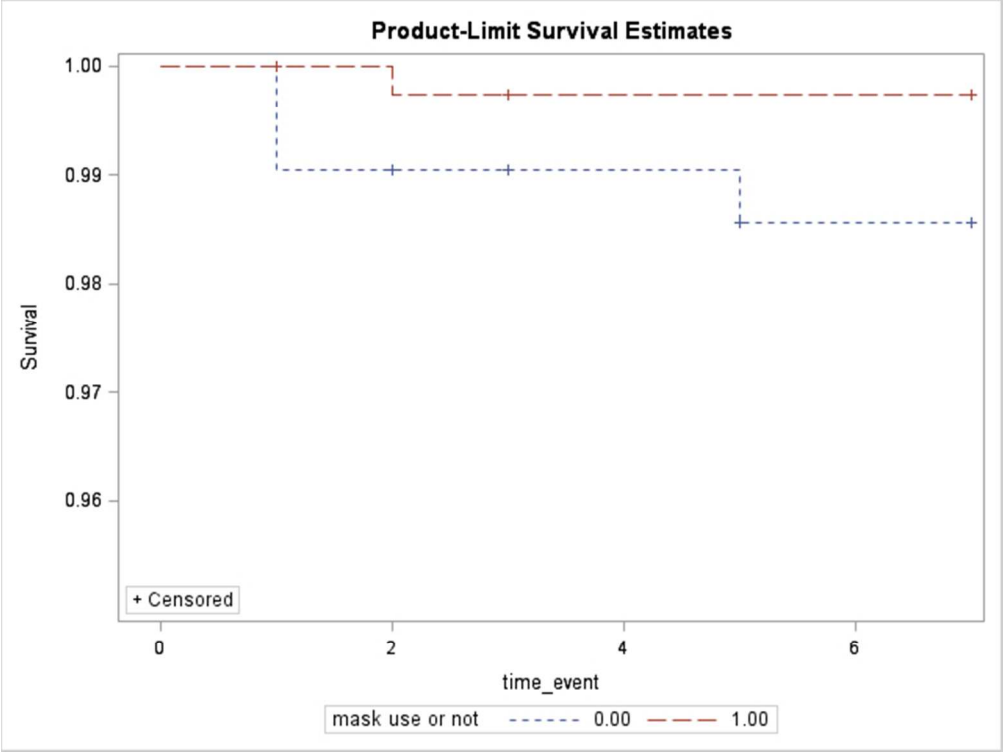
Survival curves for medical mask vs control arms (2b) ILI



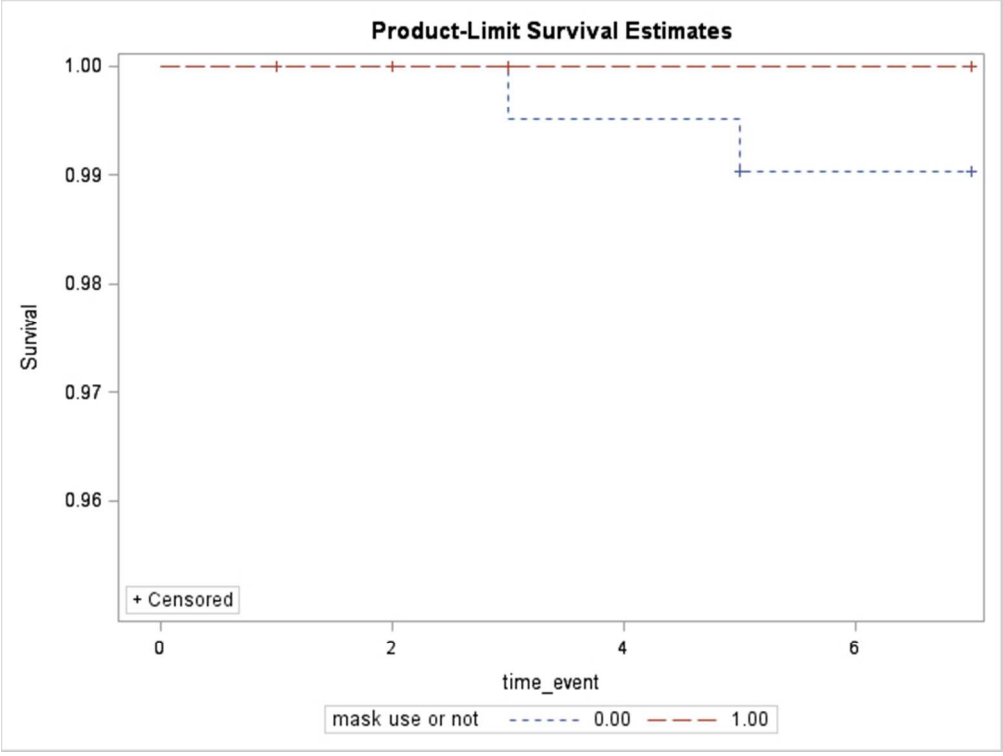
Survival curves for medical mask vs control arms (2c) laboratory-confirmed viral respiratory infections



Survival curves for mask vs no mask group (3a) CRI



Survival curves for mask vs no mask group (3b) ILI



Survival curves for mask vs no mask group (3c) laboratory-confirmed viral respiratory infections

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[1,2]	See table 2	2-3
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	5-6
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	6
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		**NA**
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	7
	4b	Settings and locations where the data were collected		**7**
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and	Whether outcome measures pertain to the cluster level, the individual participant level or both	7

		when they were assessed		
	6b	Any changes to trial outcomes after the trial commenced, with reasons		**Yes. Laboratory-confirmed bacterial colonization was an outcome in the protocols however we did could not test due to a lack of funding.**
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	11
	7b	When applicable, explanation of any interim analyses and stopping guidelines		**NA**
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		**7**
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	NA
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	

	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	7
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	7-8
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		**NA**
	11b	If relevant, description of the similarity of interventions		**NA**
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		**12**
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	12 and Figure 1
	13b	For each group, losses and exclusions after randomisation, together with	For each group, losses and exclusions for both clusters and	13

		reasons	individual cluster members	
Recruitment	14a	Dates defining the periods of recruitment and follow-up		**6**
	14b	Why the trial ended or was stopped		**6**
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	Table1 and table 2
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	Table 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		**Table 2**
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		**Table 4 and table 5**
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[3])		**NA**
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		**17-18**
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	17-18

Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	**15-17**
Other information			
Registration	23	Registration number and name of trial registry	**4**
Protocol	24	Where the full trial protocol can be accessed, if available	**4**
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	**4**

** Note: page numbers optional depending on journal requirements*

Table 2: Extension of CONSORT for abstracts[1,2] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	**Identification of study as cluster randomised**
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	**Eligibility criteria for clusters**
Interventions	Interventions intended for each group	
Objective	Specific objective or hypothesis	**Whether objective or hypothesis pertains to the cluster level, the individual participant level or both**
Outcome	Clearly defined primary outcome for this report	**Whether the primary outcome pertains to the cluster level, the individual participant level or both**
Randomization	How participants were allocated to interventions	**How clusters were allocated to interventions**
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	
Results		
Numbers randomized	Number of participants randomized to each group	**Number of clusters randomized to each group**
Recruitment	Trial status[1]	
Numbers analysed	Number of participants analysed in each group	**Number of clusters analysed in each group**
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	**Results at the cluster or individual participant level as applicable for each primary outcome**
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	
Trial registration	Registration number and name of trial register	
Funding	Source of funding	

[1] Relevant to Conference Abstracts

REFERENCES

1 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283

2 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20

3 Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.

BMJ Open

Cluster randomised controlled trial to examine medical mask use as source control for people with respiratory illness

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-012330.R3
Article Type:	Research
Date Submitted by the Author:	02-Dec-2016
Complete List of Authors:	MacIntyre, Raina; University of New South Wales, Zhang, Yi; Institute for Infectious Disease and Endemic Disease Control, Beijing Center forDisease Prevention and Control (CDC) Chughtai, Abrar; Univesity of New South Wales, School of Public Health and Community Medicine Seale, Holly; University of New South Wales, School of Public Health and Community Medicine Zhang, Daitao; Institute for Infectious Disease and Endemic Disease Control, Beijing Center forDisease Prevention and Control (CDC) Chu, Yanhui; Xicheng District Center for Diseases Prevention and Control, Beijing , China Zhang, Haiyan ; Dongcheng District Center for Diseases Prevention and Control, Beijing, China Rahman, Bayzidur; University of New South Wales, School of Public Health and Community Medicine Wang, Quanyi; Institute for Infectious Disease and Endemic Disease Control, Beijing Center for disease prevention and control
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Infectious diseases
Keywords:	Mask, Influenza, Infection control < INFECTIOUS DISEASES

Cluster randomised controlled trial to examine medical mask use as source control for people with respiratory illness

Chandini Raina MacIntyre, Yi Zhang, Abrar Ahmad Chughtai, Holly Seale, Daitao Zhang, Yanhui Chu, Haiyan Zhang, Bayzidur Rahman, Quanyi Wang

School of Public Health and Community Medicine UNSW Medicine University of New South Wales Sydney Australia and College of Public Service & Community Solutions, Arizona State University, Phoenix, Arizona, United States, The Beijing Centre for Disease Prevention and Control Beijing China, XiCheng district CDC Beijing China, Dongcheng district CDC Beijing China, Chandini Raina MacIntyre Professor and Head of School of Public Health and Community Medicine University of New South Wales, Yi Zhang Doctor The Beijing Centre for Disease Prevention and Control, Abrar Ahmad Chughtai Post doctorate Research Fellow University of New South Wales, Holly Seale Associate Lecturer University of New South Wales, Daitao Zhang, Doctor The Beijing Centre for Disease Prevention and Control, Yanhui Chu Doctor Xicheng District Center for Diseases Prevention and Control, Haiyan Zhang Doctor Dongcheng District Center for Diseases Prevention and Control, Bayzidur Rahman, Senior Lecturer University of New South Wales, Quanyi Wang Professor The Beijing Centre for Disease Prevention and Control

Corresponding author

Dr. Abrar Ahmad Chughtai

Level 2, Samuels Building, School of Public Health & Community Medicine, UNSW Medicine University of New South Wales, Sydney 2052, Australia

Telephone: +61 (2) 9385 3129 Fax: +61 (2) 9313 6185

Email: doctorahmad75@gmail.com

ABSTRACT

Rationale: Medical masks are commonly used by sick individuals with influenza-like illness (ILI) to prevent spread of infections to others, but clinical efficacy data are absent.

Objective: Determine whether medical mask use by sick individuals with ILI protects well contacts from related respiratory infections.

Setting: Six major hospitals in two districts of Beijing, China

Design: Cluster randomised controlled trial

Participants: 245 index cases with ILI

Intervention: Index cases with ILI were randomly allocated to medical mask (n=123) and control arms (n=122). As 43 index cases in the control arm also used a mask during the study period, an as-treated post-hoc analysis was performed by comparing outcomes among household members of index cases who used a mask (mask group) with household members of index cases who did not use a mask (no-mask group).

Main outcome measure: Primary outcomes measured in household members were clinical respiratory illness, ILI, and laboratory-confirmed viral respiratory infection.

Results:

In intention-to-treat analysis, rates of clinical respiratory illness (RR 0.61, 95% CI 0.18 to 2.13), ILI (RR 0.32, 95% CI 0.03 to 3.13) and laboratory-confirmed viral infections (RR 0.97, 95% CI 0.06 to 15.54) were consistently lower in the mask arm compared to control, although not statistically significant. A post-hoc comparison between the mask versus no-

mask groups showed a protective effect against clinical respiratory illness, but not against ILI and laboratory-confirmed viral respiratory infections.

Conclusion:

The study indicates a potential benefit of medical masks for source control, but is limited by small sample size and low secondary attack rates. Larger trials are needed to confirm efficacy of medical masks as source control.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths

1. Medical masks are commonly used to prevent spread of infection from sick individuals to others, however data on the clinical efficacy of this approach are sparse.
2. A cluster randomised control trial was conducted to examine the efficacy of medical masks as source control.

Limitations

3. The sample size was small and the study was underpowered to detect a statistically significant difference in outcome in the intention-to-treat analysis.
4. Removal of masks in the intervention arm during meal times may have reduced efficacy and biased the results toward the null.

Trial registration: Australian New Zealand Clinical Trials Registry (ANZCTR), ACTRN12613000852752 (http://www.anzctr.org.au).

Funding source: This study was supported by UNSW Goldstar award.

INTRODUCTION

Medical masks are commonly used in healthcare settings for two main purposes: 1) by well healthcare workers (HCWs) to protect them from infections transmitted by droplet route and splash and spray of blood and body fluids; and 2) by sick individuals to prevent transmission to others (source control) (1, 2). There are currently major gaps in our knowledge about the impact of masks on the transmission of respiratory infections (3). Most clinical trials have been focused on the protection of the well wearer, rather than on source control (3). Cloth and medical masks were originally developed as source control to prevent contamination of sterile sites by the wearer in operating theatres (OTs) (4, 5), however their effectiveness in preventing surgical site infections is yet to be proven (6-8).

Although masks are also widely used in the community to prevent spread of infection from sick and infectious people (9-13), the majority of data on their use are observational and derived from outbreaks and pandemics. Among the 9 randomized controlled trials (RCTs) in household and community settings to date (3), only one examined the role of masks as source control and was inconclusive (14). In other clinical trials, masks were either used by both sick patients (index cases as source control) and their household members (15-17) or used only by household members (18-20). Most of these studies failed to show any efficacy of mask use in preventing spread of infections from the sick individuals.

Masks are also used to prevent surgical site infections in the operating theatre (OT) (3), although most studies failed to show any efficacy against this indication (6-8, 21). Only one clinical trial reported high infection rates after surgery if masks were not used by the surgeon in the OT (22). Among the five clinical trials in the healthcare setting to test the efficacy of masks/ respirators as respiratory protection (3), none examined the use of masks

as source control. Laboratory studies generally support the use of medical masks to prevent spread of infections from influenza and TB patients to their contacts (23-25).

Mask use as source control in healthcare settings has now been included in standard infection control precautions during periods of increased respiratory infection activity in the community, yet there is no clinical efficacy evidence to support this recommendation. The aim of this study was to determine whether medical mask use by people in a community setting with influenza-like illness (ILI) protects well contacts from infection.

METHODS

Design

An RCT was conducted in fever clinics in six major hospitals in two districts of Beijing, China. The fever clinics are outpatient departments for the assessment and treatment of febrile patients. The recruitment of participants started on 18th November 2013 and completed on 20 January 2014. Adults who attended the fever clinic were screened by hospital staff to identify if they were eligible for the study. A study staff member approached eligible patients when they presented in the clinic and invited them to participate in the study. Recruited patients meeting the case definition of ILI (see below) were referred to as index cases, which was the first case in a potential chain of infection transmission.

Eligibility

Patients 18 years and older (index cases) with ILI (defined as fever ≥38ºC plus one respiratory symptom including cough, nasal congestion, runny nose, sore throat or sneezes) who attended a fever outpatient clinic during the study period, had no history of ILI amongst

household members in the prior 14 days and who lived with at least two other people at home were recruited for the study. ILI was used as a selection criterion to achieve high specificity for index cases. Patients who were unable or refused to give consent, had onset of symptoms >24 hours prior to recruitment, were admitted to hospital, resided in a household with less than two other people, or have other ill household members at home were excluded from the study.

Randomisation

After providing informed consent, 245 index cases were included and randomly allocated to intervention (mask) and control (no mask) arms. A research team member (YZ) performed the random allocation sequence using Microsoft Excel and doctors enrolled the participants randomly to intervention and control arms. Patients had an equal chance to be in the either intervention or control arm. One hundred and twenty three index cases and 302 household contacts were included in the mask (source control) arm and 122 index cases and 295 household contacts were included in control arm (Figure 1). Cases and their household contacts were assigned together as a cluster to either intervention or control arm.

Intervention

The mask or no mask intervention was applied to the index cases and respiratory illness was measured in household contacts. Index cases (patients with ILI) in the intervention arm wore a medical mask at home. Index cases were asked to wear a mask (3M 1817 surgical mask) whenever they were in the same room as a household member or a visitor to the household. They were allowed to remove their masks during meal times and while asleep. Index cases were shown how to wear the mask and instructed to wash their hands when donning and

doffing the mask. Index cases were provided with three masks per day for 7 days (21 masks in total). They were informed that they could cease wearing a mask once their symptoms resolved. Index cases in the control arm did not receive any intervention. Mask use by other household members was not required and not reported.

Outcome measures

Respiratory illness outcomes were measured in household contacts of the index cases. Primary endpoints measured in household contacts included: (1) clinical respiratory illness (CRI), defined as two or more respiratory symptoms (cough, nasal congestion, runny nose, sore throat or sneezes) or one respiratory symptom and a systemic symptom (chill, lethargy, loss of appetite, abdominal pain, muscle or joint aches) ; (2) ILI, defined as fever ≥38ºC plus one respiratory symptom ; and (3) laboratory-confirmed viral respiratory infection, defined as detection of adenoviruses, human metapneumovirus, coronaviruses 229E/NL63 and OC43/HKU1, parainfluenzaviruses 1, 2 and 3, influenza viruses A and B, respiratory syncytial virus A and B, or rhinovirus A/B by nucleic acid testing (NAT) using a commercial multiplex polymerase chain reaction (PCR) (Seegen, Inc., Seoul, Korea) (26-28).

If any respiratory or systemic symptoms occurred in household members, index cases were instructed to notify the study coordinator. Symptomatic household members were asked to complete "sick follow-up" questionnaires and anyone who met the CRI definition was tested for laboratory-confirmed viral respiratory infections.

Data collection and follow-up

At baseline detailed clinical and demographic information including household structure was collected from index cases and their household members. This included age, sex, smoking history, comorbidities, medications, hand washing practices, influenza vaccination and normal practices around the use of masks.

Follow-up period (7 days): Each index case was asked to keep a diary to record activities, symptoms and daily temperatures for seven days. Symptoms in the household members were also recorded in the diary cards and index cases were asked to report any symptom. The index cases were asked to contact the study coordinator if any of the following symptoms appeared in household members: cough, nasal congestion, runny nose, sore throat, sneezes, chill, lethargy, loss of appetite, abdominal pain and muscle or joint aches. The study coordinator then assessed the household member and completed a follow-up survey. Samples were obtained from all symptomatic cases. All index cases in the intervention and control arms were also asked to document compliance with mask use (27, 28). Diary cards to record mask use were given to each index case, and they were asked to carry them during the day. Diary cards were returned to the investigators at the end of the study. The study coordinator also contacted index cases via telephone on every alternate day to check whether any household member developed symptoms. Assessors were not blinded, because the intervention (mask wearing) was visible. However, laboratory testing was blinded.

Sample Collection and Laboratory Testing

Samples were collected from index patients at the time of recruitment and from symptomatic household members during follow-up. Household members were provided with an information sheet and written consent was sought before sampling. Only those household members who provided consent were swabbed. If the sick household member was aged <18years, consent was obtained from a parent or guardian. Swabs were taken at the home by trained investigators.

Double rayon-tipped, plastic-shafted swabs were used to swab both tonsilar areas and the posterior pharyngeal wall of symptomatic subjects. The swabs were then transported immediately after collection to the Beijing CDC laboratories, or stored at 4ºC within 48 hrs if transport was delayed.

Viral DNA/RNA was extracted from each respiratory specimen using the Viral Gene-spin TM Kit (iNtRON Biotechnology, Inc., Seoul, Korea) according to the manufacturer's instructions. Reverse transcription was performed using the RevertAidTM First Strand cDNA Synthesis Kit (Fermentas, ON, Canada) to synthesize cDNA. Multiplex PCR was carried out using the Seeplex® RV12 Detection Kit (Seegen, Inc., Seoul, Korea) to detect adenoviruses, human metapneumovirus, coronavirus 229E/NL63 and OC43/HKU1, parainfluenzaviruses 1, 2 or 3, influenza viruses A or B, respiratory syncytial virus A or B, and rhinovirus A/B. A mixture of 12 viral clones were used as a positive control template, and sterile deionized water was used as a negative control. Viral isolation by MDCK cell culture was undertaken for some of the influenza samples that were NAT positive. Specimen processing, DNA/RNA extraction, PCR amplification, and PCR product analyses was conducted in different rooms to avoid cross-contamination.

Sample size

In this cluster randomized design, the household was the unit of randomization and the average household size was three people. Assuming the attack rate of CRI in the control households was 16-20% (based on the results of a previously published household mask trial) (18), with 5% significance level and 85% power, minimum relative risk of 0.5 (intervention/control), 385 participants were required in each arm, which was composed of 118 households and on average, three members per household. In this calculation, we assumed that the intracluster correlation coefficient (ICC) was 0.1. An estimated 250 patients with ILI were recruited into the study to allow for possible index case dropout during the study.

Data analysis

Descriptive statistics were compared in mask and control arms and respiratory virus infection attack rates were quantified. Data from the diary cards were used to calculate person-days of infection incidence. Primary endpoints were analysed by intention to treat across the study arms and ICC for clustering by household was estimated using clchi2 command in Stata (29). Relative risks were calculated for the mask arm. Kaplan-Meier survival curves were generated to compare the survival pattern of outcomes across mask and control arms. Differences between the survival curves were assessed through Log-rank test. The analyses were conducted in individual level and hazard ratios (HR) were calculated using Cox proportional hazards model after adjusting for clustering by household by adding a shared frailty to the model. Due to very few outcome events encountered a multivariable Cox model was not appropriate. We checked the effect of individual potential confounders on the outcome variable fitting univariable Cox models. Because there were 10 cases of CRI,

we included this variable in a multivariable cluster adjusted Cox model. Multivariate analyses were not performed for ILI and laboratory-confirmed viruses because of low numbers.

A total of 43 index cases in the control arm also used a mask during the study period (at least one hour per day) and 7 index cases in the masks arm did not use a mask at all, so a post-hoc sensitivity analysis was carried out to compare outcomes among household members of index cases who used a mask (hereafter "mask group"), with those of index cases who did not use a mask (hereafter "no-mask group"). All statistical analyses were conducted using Stata version 13 (30).

Ethics approval

Ethics approval was obtained from the Beijing Center for Disease Prevention and Control IRB and the Human Research Ethics Committee of the University of New South Wales (UNSW), Australia (HREC approval number HC13236).

RESULTS

A total of 245 index patients were randomised into the mask arm (n=123) or the control arm (n=122). The mask arm had on average 2.5 household contacts per index case (n=302), while the control arm had 2.4 household contacts per index cases (n=295). Characteristics of index cases and household members are presented in table 1. There was no significant difference between arms, and most characteristics, including medication use (data not shown), were generally similar. Viruses were isolated from 60% (146/245) index cases. Influenza was the most common virus isolated from 115 (47%) cases - Influenza A - 100, Influenza B - 11 and Influenza A&B - 4. Other viruses isolated from index cases were, rhinovirus (14), NL63 (12)

and C229E (7). More than one virus was isolated in 48 (20%) index cases, including 17 coinfections with influenza.

Table 2 shows the intention to treat analysis. CRI was reported in 4 (1.91/1000 person-days) household members in the mask arm, compared to 6 household members (2.95/1000 person-days) in the control arm (RR 0.65, 95% CI 0.18 to 2.29). Only 1 case (0.48/1000 person-days) of ILI was reported in the mask arm, compared to 3 cases (1.47/1000 person-days) in the control arm (RR 0.32, 95% CI 0.03 to 3.11). Two laboratory confirmed infections were identified among symptomatic household members from separate household. One household member had the same infection (influenza H1N1) as the respective index case. Rhinovirus was isolated from other household member. However no pathogen was isolated from respective index case. The two cases of laboratory-confirmed viral respiratory infections of household members occurred in separate study arms (RR 0.97, 95% CI 0.06 to 15.5). The Kaplan-Meier curves showed no significant differences in the outcomes between two arms (P-value > 0.050) (Figure 2).

Duration of contact of index cases with household members was 10.4 hours and 11.1 hours in mask and control arms respectively. On average, participants in the mask arm used a mask for 4.4 hours, while participants in the control arm used a mask for 1.4 hours. In a univariable Cox model only the age of household contact was significantly associated with the CRI (Table 3). There was no association between mask use by the index cases and rates of infectious outcomes in household members (Table 3). Although the risks of CRI (RR 0.61, 95% CI 0.18 to 2.13), ILI (RR 0.32, 95% CI 0.03 to 3.13) and laboratory-confirmed viral infections (RR 0.97, 95% CI 0.06 to 15.54) were lower in the mask arm, the difference was not statistically significant.

Tables 4 & 5 show a sensitivity analysis comparing outcomes among household members of index cases using a mask ("mask group"), with those of index cases who did not use a mask ("no-mask group"). Overall, 159 index cases (65%) used a mask during the trial period including 43 subjects from the control arm. Three hundred and eighty seven household members were included in the mask group and 210 were included in the no-mask group. Rates of all outcomes were lower in the mask group, and CRI was significantly lower in the contacts of the mask group compared to the contacts of the no-mask group. The Kaplan-Meier curves (Figure 3) showed a significant difference in the rate of CRI among the mask and no-mask groups (P- 0.020).

After adjusting for the age of household contacts, the risk of CRI was 78% lower in the contacts of the mask group (RR 0.22, 95% CI 0.06 to 0.86), compared to contacts of the no-mask group. Although the risks of ILI (RR 0.18, 95% CI 0.02 to 1.73) and laboratory-confirmed viral respiratory infections (RR 0.11, 95% CI 0.01 to 4.40) were also lower in the mask group, the difference was not statistically significant.

DISCUSSION

Masks are commonly recommended as source control for patients with respiratory infections to prevent the spread of infection to others (2, 3), but data on the clinical efficacy of this approach are sparse. We did not find a significant benefit of medical masks as source control, but rates of CRI and ILI in household members were consistently lower in the mask arm compared to the control arm. The study was underpowered to detect a statistically significant difference. The additional analysis by actual mask use showed significantly lower rates of CRI in mask group compared to the no-mask group, suggesting larger trials should be conducted to further examine the efficacy of masks as source control.

Our findings are consistent with previous research in community and household settings, where the efficacy of masks as source control was measured. To date, only one RCT has been conducted in the community setting to examine the role of masks in preventing spread of infection from wearers (3). Canini et al. conducted an RCT in France during the 2008–2009 influenza season and randomised index patients into medical mask (52 households and 148 contacts) and control arms (53 households and 158 contacts). ILL was reported in 16.2% and 15.8% contacts in the intervention and control arms, respectively, and the difference was not statistically significant (mean difference 0.40%, 95%CI: -10% to 11%, P= 1.00). The trial was concluded early due to low recruitment and the subsequent influenza A (H1N1)pdm09 pandemic (14). In addition, masks were also used by both index cases and household members in some community based RCTs with mixed interventions (15, 16). Cowling et al. conducted two RCTs in Hong Kong to examine the efficacy of masks, and index cases were randomised into medical mask, medical mask plus hand hygiene, hand hygiene and control arms. Both index cases and household members used masks. The rates of laboratory-confirmed influenza and ILI were the same in the intervention and control groups in the intention to treat analysis (15). However, in the second trial mask use with hand hygiene was protective in household contacts when the intervention was applied within 36 hours of onset of symptoms in the index case (OR 0.33, 95% CI, 0.13 to 0.87) (16). As masks were used by both sick patients and their household members in these studies, the effect of mask being “source control” is more difficult to precisely quantify.

Masks are not designed for respiratory protection and are commonly used in the healthcare setting to prevent spread of infections from the wearer, whether worn by a sick patient or well staff member (1, 3). One such use is the wearing of masks by well surgeons and other

OT staff to protect patients from contamination during surgery. Presumably, the exhaled pathogen load would be much higher in a sick patient compared to a well surgeon, and therefore the use of a mask for source control in sick patients may have more benefit than OT use of source control.

This study has some limitations. The sample size was small and the study may have been underpowered to detect a statistically significant difference in outcome in the intention-to-treat analysis. Post-hoc analysis however, showed a potential benefit of medical masks for source control. It is possible that infection transmission may have occurred during meal times (when patients were not required to wear a mask). This would have the effect of biasing the results toward the null. In the sample size calculations, we assumed 16-20% attack rate of CRI in the control arm, based on the results of a previously published household mask trial (18). However the secondary attack rates were much lower in this study which might be due to testing only symptomatic cases.

In a univariable Cox model only the age of household contact was significantly associated with the CRI. All other variables were uniformly distributed among the study arms so we only adjusted for age of household contact in the analysis of CRI as an outcome. Multivariate analyses were not performed for ILI and laboratory-confirmed viruses. However some variables may have impact on the number of events. For example the rates of hand hygiene were higher among the "control" arm compared to the mask arm (109/122, 89.3% vs. 98/123, 79.7%) which may have had an impact on the number of outcome events. Due to low event rates and non-significant difference of hand hygiene among the two arms, we did not adjust for hand hygiene in any analysis. Further, inclusion of hand hygiene in the model did not change the HR. Finally, post-hoc analyses are potentially biased due to loss of

randomisation and it was added as a sensitivity analysis in this study because of deviations from protocol in mask wearing.

Despite a lack of evidence, most health organisations and countries recommend the use of masks by sick patients as source control (1, 2). Masks are used commonly by TB patients, although clinical trials have not been conducted for this indication. There is a need to conduct larger trials to confirm the suggestion of benefit in our study. If source control is effective in reducing hospital transmission of infection, this may have a practical benefit to mitigate the problem of poor compliance with mask wearing among well HCWs (3). Compliance with any intervention for someone who is well and asymptomatic is far more challenging than compliance in people who are unwell (31), so source control may have an important role in hospital infection control. Reducing the transmission of respiratory pathogens by source patients could also have further benefits in the community in preventing transmission of infection to close contacts such as those in the same household, and should be studied further.

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COMPETING INTERESTS

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare that;

1. Professor C. Raina MacIntyre: Raina MacIntyre has held an Australian Research Council Linkage Grant with 3M as the industry partner, for investigator driven research. 3M have also contributed supplies of masks and respirators for investigator-driven clinical trials. She has received research grants and laboratory testing as in-kind support from Pfizer, GSK and Bio-CSL for investigator-driven research.
2. Dr Holly Seale had a NHMRC Australian based Public Health Training Fellowship at the time of the study (1012631). She has also received funding from vaccine manufacturers GSK, bio-CSL and Saniofi Pasteur for investigator-driven research and presentations.
3. Dr. Abrar Chughtai had testing of filtration of masks by 3M for PhD.

The remaining authors declare that they have no competing interests and have no non-financial interests that may be relevant to the submitted work."

ACKNOWLEDGEMENTS

Thanks to the staff at the Beijing Centre for Disease Control and hospitals staff. We also acknowledge the support of patients and their families. This study was supported by UNSW Goldstar award.

CONTRIBUTORSHIP STATEMENT

CRM: lead investigator, responsible for conception and design of the study, analysing data and writing the manuscript; Yi Zhang: YZ: implementation and database management, AAC: statistical analysis and drafting of manuscript; HS, DZ, YC, HZ: recruitment and training, manuscript revision, Bayzidur Rahman: contributed to the statistical analysis and revision of manuscript, QW: implementation, contribution to design, analysis and drafting of paper.

TRANSPARENCY DECLARATION

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA SHARING STATEMENT

No additional data available

FIGURE LEGENDS

Figure1. Consort diagram of recruitment and follow-up

Figure 2: Survival curves for medical mask vs control arms (2a, 2b and 2c)

Figure 3: Survival curves for mask vs no mask group (3a, 3b and 3c)

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Table 1: Demographic and other characteristics of the index cases and household members

Variable	Mask arm (% and 95% CI)	Control arm (% and 95% CI)
Index case (number)	**123**	**122**
Gender (male)	56/123 45.5% (37.0% to 54.3)	45/122 36.9% (28.8% to 45.7%)
Age (mean)	40.2 (37.6 to 42.8)	39.7 (37.3 to 42.0)
Education (Under/postgraduate)	78/123 63.4% (54.6%-71.4%)	74/122 60.7% (51.8 to 68.9%)
Smoker (Current/Ex)	29/123 23.6% (16.9% to 31.8%)	26/122 21.3% (15.0% to 29.4%)
Pre-existing illness*	21/123 17.1% (16.2% to 31.0%)	16/122 13.1% (8.2% to 20.2%)
Influenza vaccination (Yes)	5/123 4.1% (1.7% to 9.2%)	5/122 4.1% (1.8% to 9.2%)
Hand washing (most/all times)	98/123 79.7% (71.7% to 85.8%)	109/122 89.3% (82.6% to 93.7%)
Average hour of home stay†	16.6 (15.9 to 17.3)	16.6 (15.9 to 17.3)
Average hour mask wearing†	4.4 (3.9 to 4.9)	1.4 (0.9 t0 1.8)
Household (members)	**302**	**295**
Number of house hold per arm	2.5	2.4
Gender (male)	149/302 49.3% (43.4% to 24.6%)	168/295 56.9% (51.6% to 62.9%)
Influenza vaccination (Yes) ‡	22/298 7.4% (4.9% to 10.9%)	30/285 10.5% (7.1% to 14.6%)
Age (mean)	38.3 (36.0 to 40.5)	36.4 (34.1 to 38.8)

*. *Includes asthma, chronic obstructive pulmonary disease, diabetes, ischemic heart disease, immune-compromised and others*

† *Variable was created by taking average hours over the trial period.*

‡ *Missing data for 14 cases.*

Table 2: Number and proportion of household members reporting primary outcomes, by randomization arm and intention-to-treat analysis (n=597)*

	Clinical respiratory illness (CRI) No (rate person-days)	RR (95% CI)	Influenza-like illness (ILI) No (rate person-days)		Laboratory-confirmed viral respiratory infections No (rate person-days)	RR (95% CI)
Mask arm**	4/2098 (1.91/1000)	0.65 (0.18-2.29)	1/2098 (0.48/1000)	0.32 (0.03-3.11)	1/2098 (0.48/1000)	0.97 (0.06-15.5)
Control arm***	6/2036 (2.95/1000)	Ref	3/2036 (1.47/1000)	Ref	1/2036 (0.49/1000)	Ref

* House hold members (mask arm 302 and control arm 295)
** Intracluster correlation coefficients is < 0.001
*** Intracluster correlation coefficients is < 0.001

Table 3: Hazard ratios from shared frailty Cox proportional hazards model for household members in masks vs. control arms (n=597)*

	Clinical respiratory illness (CRI) HR (95% CI)**	Influenza-like illness (ILI) HR (95% CI)**	Laboratory-confirmed viral respiratory infections HR (95% CI)**
Masks arm (Index case)	0.61 (0.18-2.13)	0.32 (0.03-3.13)	0.97 (0.06-15.54)
Control arm (Index case)	Ref	Ref	Ref
Age (Household)	1.03 (1.01-1.05)		

* House hold members (mask arm 302 and control arm 295)
** Multivariate analysis was performed as there were 10 cases of CRI and age was also significant in the univariate analysis. Multivariate analyses were not performed for ILI and laboratory-confirmed viral respiratory infections due to low number of cases.

Table 4: Number and proportion of participants reporting primary outcomes, by masks vs. no-mask groups (n=597)*

	Clinical respiratory illness (CRI) No (rate person-days)	*RR*	**Influenza-like illness (ILI) No (rate person-days)**	*RR*	**Laboratory-confirmed viral respiratory infections No (rate person-days)**	*HR*†
Mask group	3/2694 (1.11/1000)	0.23 (0.06-0.88)	1/2694 (0.37/1000)	0.18 (0.02-1.71)	0/2694 (0/1000)	0.11 (0.01-4.40)
No mask group	7/1440 (4.86/1000)	Ref	3/1440 (2.08/1000)	Ref	2/1440 (0.70/1000)	Ref

* Household members (mask group 387 and no-mask group 210)

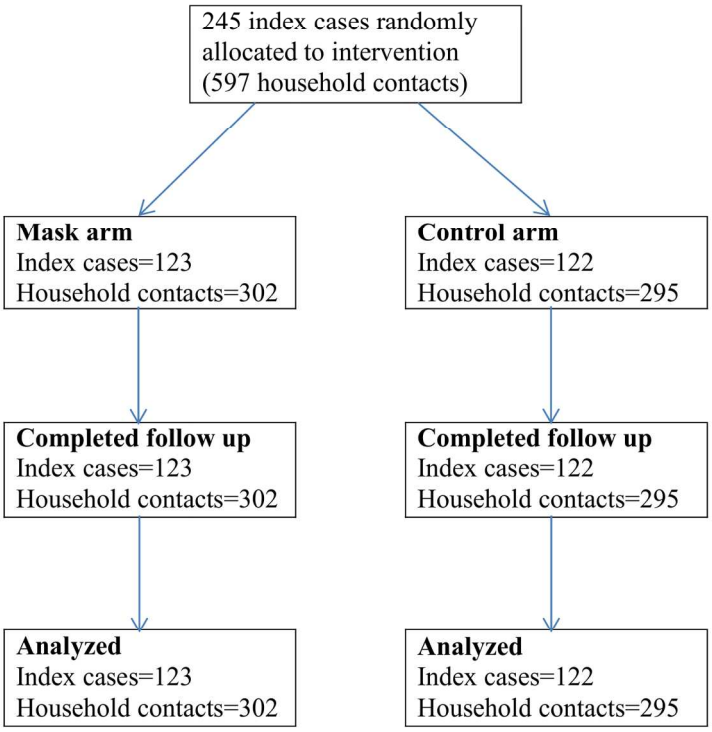
† Calculated through Cox PH methods

Table 5: Hazard ratios from Shared frailty Cox proportional hazards model for masks vs. no masks groups (no randomisation) (n=597)*

	Clinical respiratory illness (CRI) HR (95% CI)**	**Influenza-like illness (ILI) HR (95% CI)****	**Laboratory-confirmed viral respiratory infections HR (95% CI)****
Masks group (Index case)	**0.22 (0.06-0.86)**	0.18 (0.02 – 1.73)	0.11 (0.01 – 4.40)
No mask group (Index case)	Ref	Ref	Ref
Age (Household)	1.03 (1.00-1.06)		

* Household members (mask group 387 and no-mask group 210)

** Multivariate analysis was performed as there were 10 cases of CRI and age was also significant in the univariate analysis. Multivariate analyses were not performed for ILI and laboratory-confirmed viral respiratory infections due to low number of cases



Consort diagram of recruitment and follow-up

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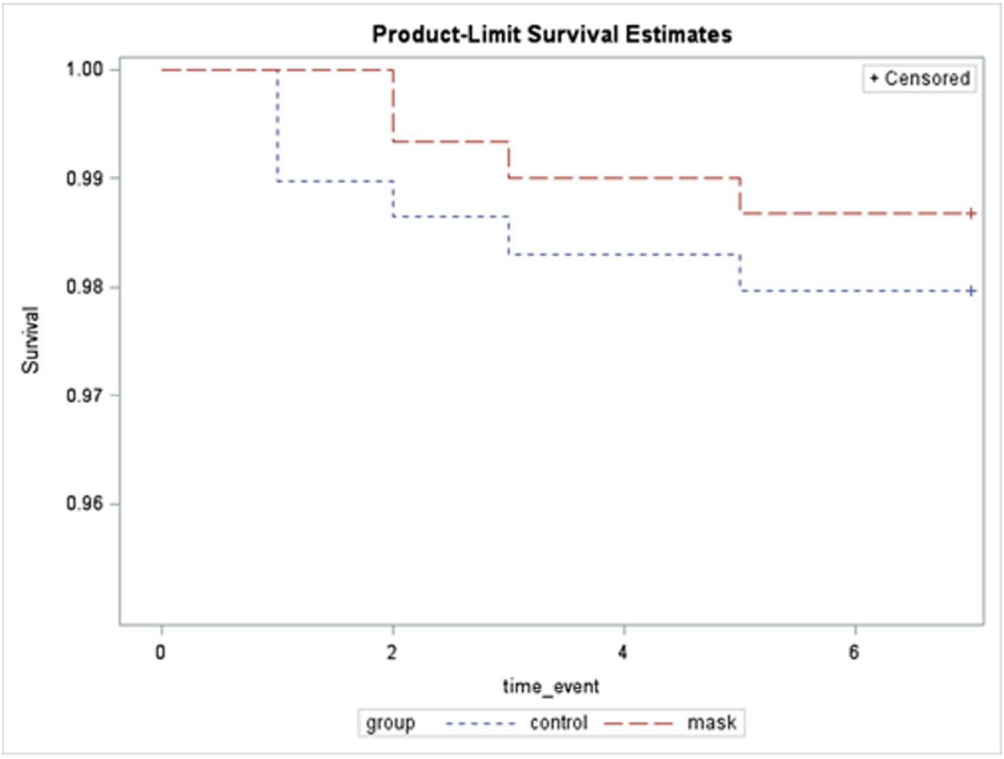
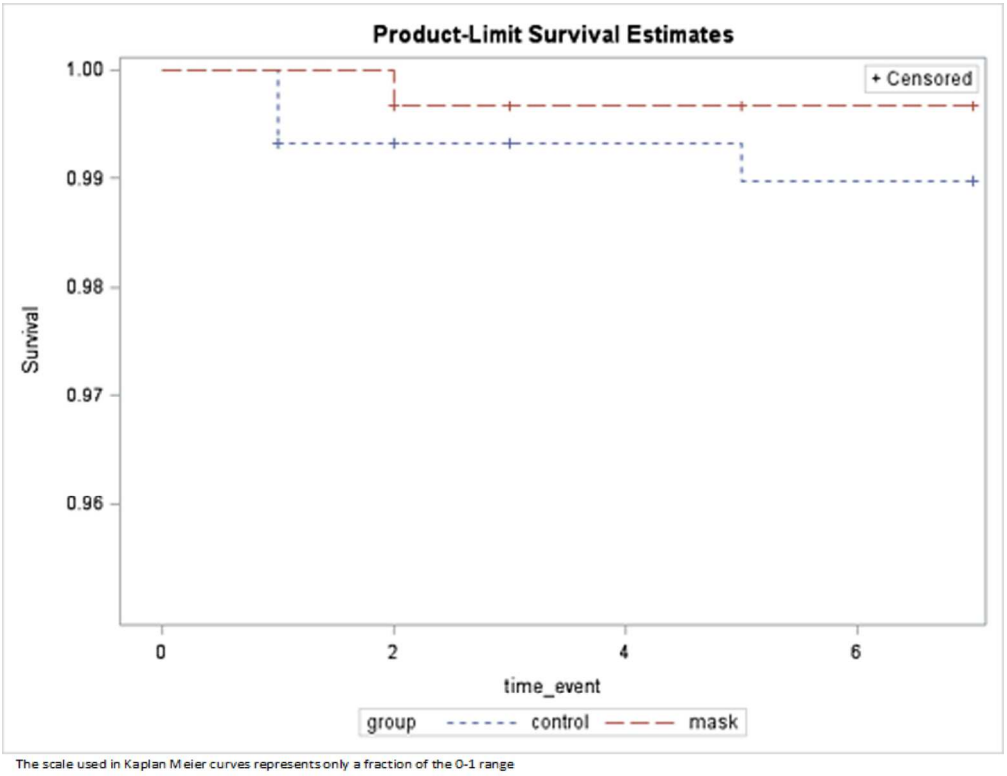


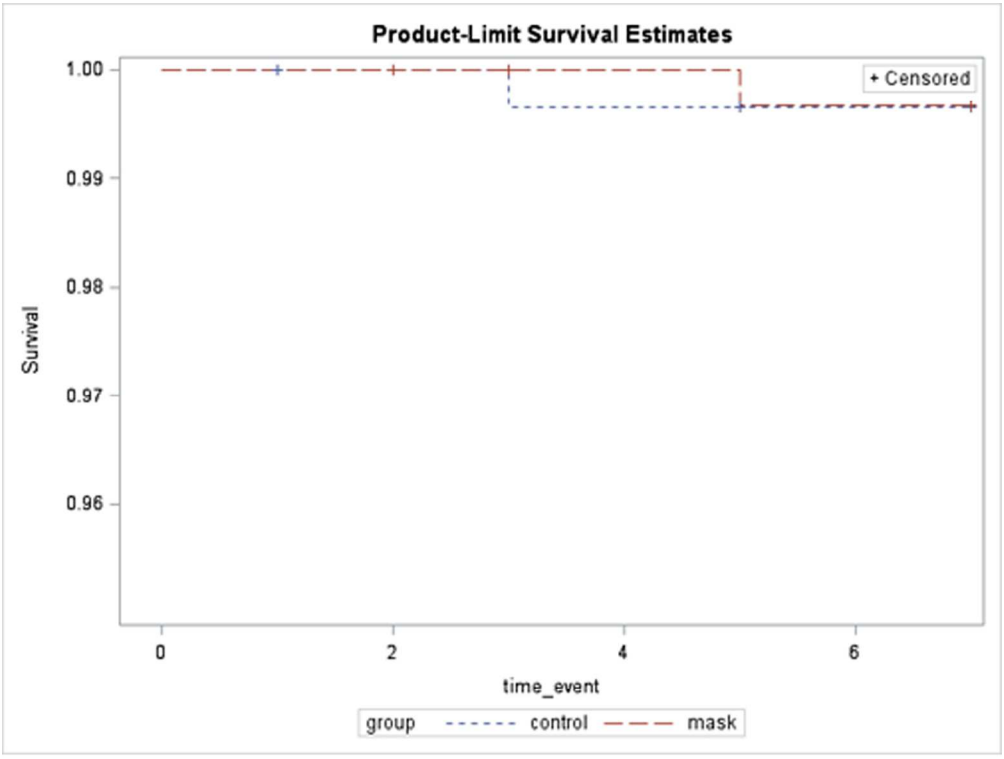
Survival curves for medical mask vs control arms (2a)

132x103mm (300 x 300 DPI)



Survival curves for medical mask vs control arms (2b)

133x104mm (300 x 300 DPI)



Survival curves for medical mask vs control arms (2c)

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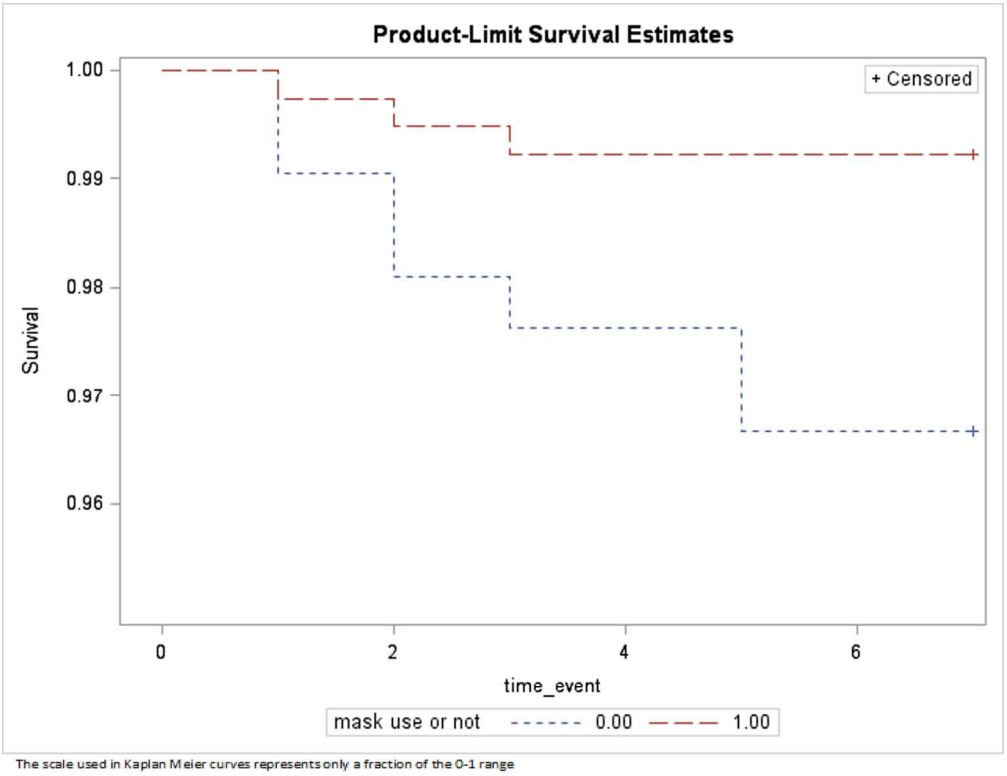
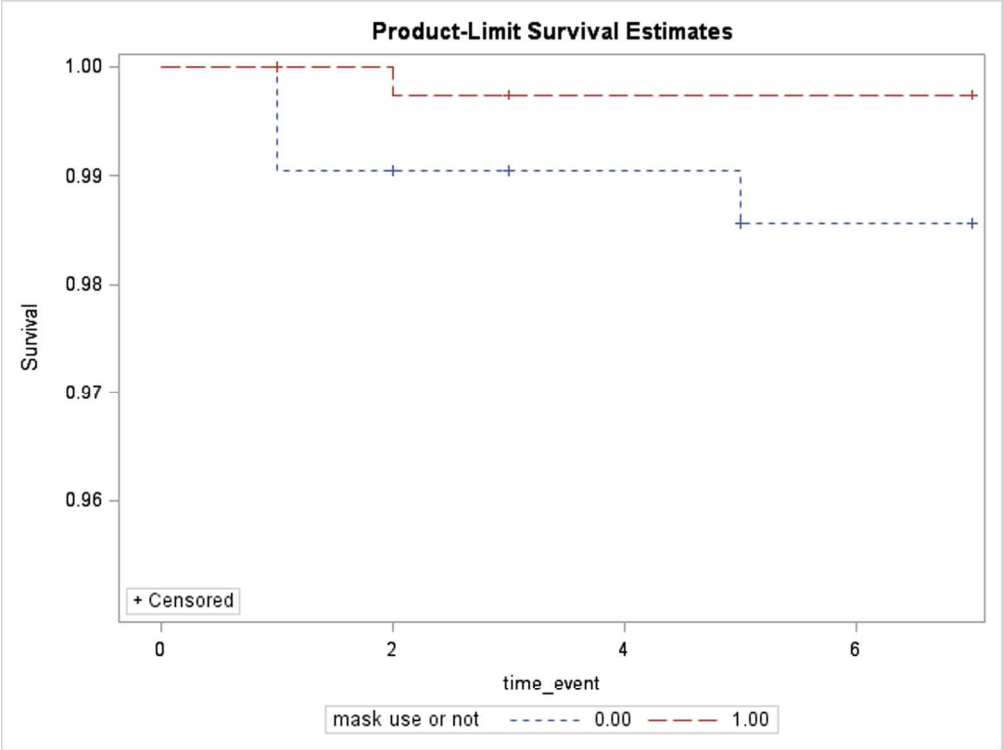


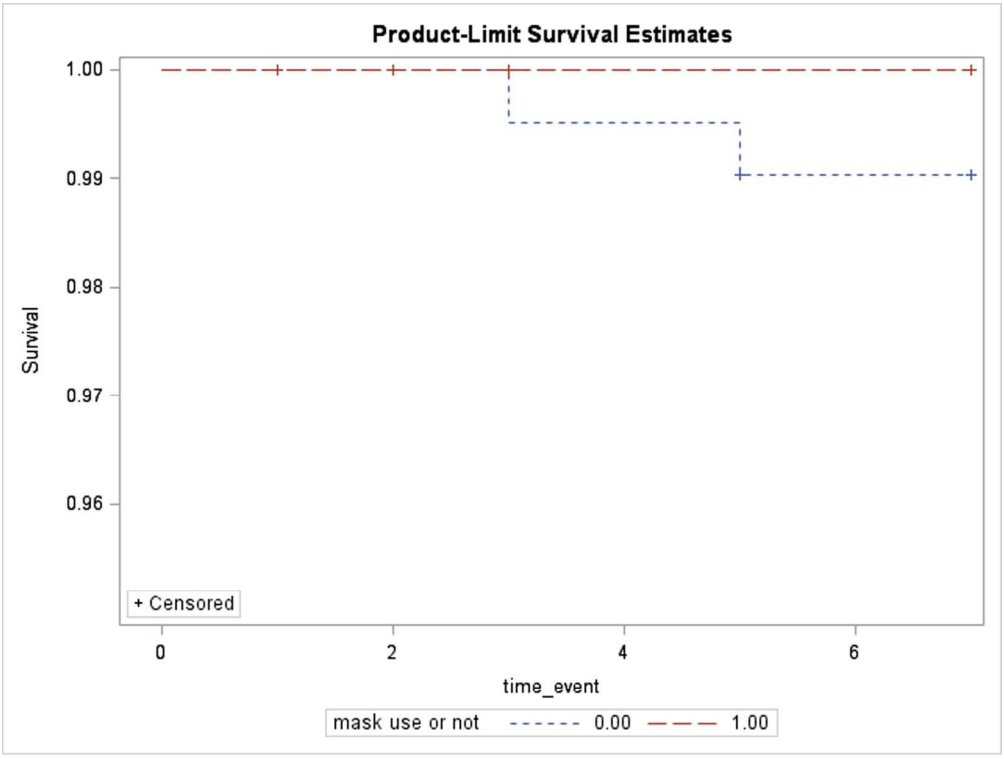
Survival curves for mask vs no mask group (3a)

131x102mm (300 x 300 DPI)



Survival curves for mask vs no mask group (3b)

132x104mm (300 x 300 DPI)



Survival curves for mask vs no mask group (3c)

132x103mm (300 x 300 DPI)

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[1,2]	See table 2	2-3
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	5-6
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	6
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		**NA**
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	7
	4b	Settings and locations where the data were collected		**7**
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and	Whether outcome measures pertain to the cluster level, the individual participant level or both	7

		when they were assessed		
	6b	Any changes to trial outcomes after the trial commenced, with reasons		**Yes. Laboratory-confirmed bacterial colonization was an outcome in the protocols however we did could not test due to a lack of funding.**
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	11
	7b	When applicable, explanation of any interim analyses and stopping guidelines		**NA**
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		**7**
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	NA
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	

	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	7
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	7-8
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		**NA**
	11b	If relevant, description of the similarity of interventions		**NA**
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		**12**
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	12 and Figure 1
	13b	For each group, losses and exclusions after randomisation, together with	For each group, losses and exclusions for both clusters and	13

		reasons	individual cluster members	
Recruitment	14a	Dates defining the periods of recruitment and follow-up		**6**
	14b	Why the trial ended or was stopped		**6**
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	Table1 and table 2
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	Table 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		**Table 2**
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		**Table 4 and table 5**
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[3])		**NA**
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		**17-18**
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	17-18

Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	**15-17**
Other information			
Registration	23	Registration number and name of trial registry	**4**
Protocol	24	Where the full trial protocol can be accessed, if available	**4**
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	**4**

** Note: page numbers optional depending on journal requirements*

Table 2: Extension of CONSORT for abstracts[1,2] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	**Identification of study as cluster randomised**
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	**Eligibility criteria for clusters**
Interventions	Interventions intended for each group	
Objective	Specific objective or hypothesis	**Whether objective or hypothesis pertains to the cluster level, the individual participant level or both**
Outcome	Clearly defined primary outcome for this report	**Whether the primary outcome pertains to the cluster level, the individual participant level or both**
Randomization	How participants were allocated to interventions	**How clusters were allocated to interventions**
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	
Results		
Numbers randomized	Number of participants randomized to each group	**Number of clusters randomized to each group**
Recruitment	Trial status[1]	
Numbers analysed	Number of participants analysed in each group	**Number of clusters analysed in each group**
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	**Results at the cluster or individual participant level as applicable for each primary outcome**
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	
Trial registration	Registration number and name of trial register	
Funding	Source of funding	

[1] Relevant to Conference Abstracts

REFERENCES

1 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283

2 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20

3 Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.