

## REVIEW

# Use of non-pharmaceutical interventions to reduce the transmission of influenza in adults: A systematic review

SHEREE M.S. SMITH,<sup>1,2</sup> SANDRA SONEGO,<sup>1</sup> GWENYTH R. WALLEN,<sup>3</sup> GRANT WATERER,<sup>4</sup>  
ALLEN C. CHENG<sup>5</sup> AND PHILIP THOMPSON<sup>6,7,8</sup>

<sup>1</sup>School of Nursing and Midwifery, University of Western Sydney, Sydney, New South Wales, and <sup>4</sup>School of Medicine and Pharmacology, Royal Perth Unit and <sup>7</sup>School of Medicine and Pharmacology, Queen Elizabeth II Unit, University of Western Australia, and <sup>6</sup>The Lung Health Clinic, Hollywood Hospital, and <sup>8</sup>Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Perth, Western Australia, and <sup>5</sup>Infectious Diseases Unit, Department of Epidemiology and Preventative Medicine, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Victoria, Australia, and <sup>2</sup>Centre for Pharmacology and Therapeutics, Imperial College, Chelsea and Westminster Campus, London, UK, and <sup>3</sup>National Institutes of Health, Clinical Center, Bethesda, Maryland, USA

## ABSTRACT

During seasonal influenza epidemics and pandemics, virus transmission causes significant public health concern. Reduction of viral transmission by non-pharmaceutical interventions (NPI) has a significant appeal and is often recommended. However, the efficacy of such interventions is unclear. A systematic literature review was undertaken to identify and evaluate the published literature on NPI efficacy to prevent human transmission of influenza virus in adults. Reviewers assessed the quality of eligible studies utilizing the Critical Appraisal Skills Programme for bias and the Scottish Intercollegiate Guidelines Network for methodological quality. Studies were assessed for risk of bias domains of random sequence generation, allocation concealment, attribution bias, selective reporting and blinding. Relevant citations of 2247 were reduced to 100 for full-text evaluation. Only seven met all selection criteria and pooled analysis was not feasible. Of the seven studies, two were randomized controlled trials (RCT) and five were cluster RCT. The main NPI studied were disinfection and hygiene; barriers; and combined NPI. However, these seven RCT had significant design flaws. Only two studies used laboratory confirmed influenza and poor statistical power was a major problem. Positive significant interventions included professional oral hygiene intervention in the elderly and hand washing. Despite the potential for NPI in preventing influenza transmission, there is very limited data available. Hand washing and dental hygiene may be useful, but other interventions have not been fully assessed. Properly designed studies evaluating large populations including 'at risk' patients and in a variety of communities are needed.

**Key words:** epidemic, influenza, non-pharmaceutical, pandemic, seasonal.

**Abbreviations:** CI, confidence interval; ILI, influenza-like-illness; NPI, non-pharmaceutical intervention; PCR, polymerase chain reaction; RCT, randomized control trials.

## INTRODUCTION

Influenza spreads between people in seasonal influenza outbreaks, epidemics and pandemics, and is of public health significance.<sup>1</sup> Reduction in person to person virus transmission may potentially reduce infection rates and decrease the morbidity and mortality associated with influenza. Three modes of influenza virus transmission have been identified<sup>2</sup> and comprise droplet transmission, contact with influenza virus surviving on hard non-porous surfaces and airborne transmission.<sup>3,4</sup> One public health strategy for the reduction in transmission relies on the implementation of non-pharmaceutical interventions (NPI). These were reported as a public health measure as early as during the 1918–1919 influenza pandemic. During this pandemic, a number of US cities implemented home quarantine for infected persons, social distancing and a reduction in public gatherings such as church meetings and closure of schools.<sup>5</sup>

NPI, currently recommended by the Centers for Disease Control and Prevention, have been categorized as either personal or community based.<sup>6,7</sup> Personal interventions<sup>7</sup> comprise encouraging people to cover their mouth and nose during coughing and sneezing, frequent hand washing and self-quarantine when a person feels unwell, whereas community-based actions<sup>6</sup> include public education through a variety of communication strategies, social distancing and restriction on public gatherings. Evidence-based simple activities such as washing surfaces and hands with detergent have previously proven successful in reducing transmission as the virus is killed by soap,

Correspondence: Sheree M.S. Smith, School of Nursing and Midwifery, University of Western Sydney, Locked Bag 1797, Penrith, Sydney, NSW 2751, Australia. Email: sheree.smith@uws.edu.au

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and so disinfectants *per se* are not necessary.<sup>8–10</sup> The use of masks and personal protective equipment may not be appropriate for non-clinical areas unless there is a medical reason to do so such as when an individual is immunocompromised.<sup>10,11</sup> Importantly, research into NPI from the recent 2009 pandemic has provided good evidence that home quarantine is feasible and acceptable; however, support for mandatory social distancing appears limited.<sup>10,12,13</sup>

Analysis and assessment of NPI has been very limited and have focussed on single specific interventions such as face masks.<sup>8</sup> Other influenza reviews<sup>14</sup> have restricted themselves to observations on a specific epidemic/pandemic or simply make suggestions of how to limit transmission based upon reviewing selected articles and appear to have merged expert opinion with what can be inferred from the literature or a selection of publications. Only one previous review<sup>10</sup> has utilized a well-designed systematic process to review the literature on physical barriers to limit the spread of respiratory viruses. Despite the limitations of these previous reviews, all agreed our knowledge base and evidence for effective interventions is poor. As such, it seemed important to undertake a detailed systematic review on the evidence for NPI that help reduce person-to-person transmission of the influenza virus. As part of this review, we sought to include evidence of NPI associated with both seasonal influenza and influenza pandemics.

## METHODS

The objective of this systematic review was to identify and evaluate the published medical literature on the efficacy of NPI to prevent human-to-human transmission of influenza virus in adults.

### Search strategy

A protocol was devised, and a systematic search of peer-reviewed literature was performed in accordance with the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.<sup>15</sup> From July 2013 to February 2014, we searched the following electronic databases: Cochrane, Medline, Pubmed, CINAHL, Embase, Sciondirect, Google Scholar and Scopus. References of publications retrieved in the search were scanned for any relevant additional citations. As well as scanning listed inclusion articles in related review papers, the *American Journal of Infection Control*, *Infection Control* and *Hospital Epidemiology, Journal of Hospital Infection and Emerging Infectious Disease* journals were also hand-searched for possible inclusion articles. Influenza and NPI search terms were combined, the search strategy adapted for the Medline database is provided in the Supplementary Table S1. Search limits applied were the English language, abstracts and humans. No restrictions were placed on publication date. Supplementary Table S2 presents the topically relevant but excluded publications in this study.

### Eligibility criteria

Articles were eligible for inclusion if they were randomized controlled trials (RCT) reporting on the

efficacy of an NPI against influenza infection. The participants of interest were adults (male and female 18 years and over) who had serologically or virologically confirmed influenza, or had clinical features of influenza, influenza-like-illness (ILI) or acute respiratory infection or were asymptomatic but at risk of contracting influenza due to health-care or community exposure. Interventions comprised any NPI, device or behaviour that was used to contain or mitigate the spread of influenza infection. Simulation models and studies conducted in controlled laboratory settings were excluded. Comparative groups included no intervention, inactive alternative intervention or standard care. Utilizing the categories of NPI outlined by Aledort *et al.*,<sup>14</sup> intervention types included contact management, index-patient management, community restrictions and surveillance. We included interventions that were either self-administered or administered by a clinician and conducted in health care, home or community settings. Studies that described purely pharmacological or vaccine-based interventions were excluded. Bundled NPI consisting of a combination of measures were considered if the interventions were composed primarily of NPI. The primary outcome of interest was evidence of decreased transmission of the influenza virus. This outcome was evaluated by the level of reduction in influenza or ILI attack rates, secondary infection ratios, viral illness severity, mortality rates and health-care utilization. Secondary outcome measures were increased awareness and education in NPI.

### Study selection and data extraction

After conducting the database searches and removing duplicates, the inclusion criteria were applied using a standardized form to assess the eligibility of the retrieved articles. This was performed by two independent reviewers (SMS, SS) by scanning titles and abstracts for relevance. Full-text articles were obtained for studies that were identified as meeting the inclusion criteria. Disagreements over inclusion articles were settled through discussion until consensus was reached, or resolved by an independent arbitrator (NM). Extraction of data was performed by the two reviewers (SMS, SS) working independently, using a pre-designed data extraction spreadsheet with categories for capturing data items such as study design, sampling, setting, participant, intervention, comparison and outcome data.

### Quality assessment

Two reviewers assessed the quality of eligible studies utilizing the Critical Appraisal Skills Programme<sup>16</sup> tools for reporting bias and the Scottish Intercollegiate Guidelines Network<sup>17</sup> checklists for methodological quality. Studies were assessed using the standard risk of bias domains; random sequence generation, allocation concealment, attribution bias, selective reporting and blinding. All studies were assigned a risk of bias grading of low, medium or high, based on the number of methodological problems identified

**Table 1** Assessment of quality rating

Quality of evidence rating	
Low	Studies with up to one methodological issue or limitation
Medium	Studies with two to three methodological issues or limitations
High	Studies with more than 3 methodological issues or limitations
Methodological quality items assessed	
Clearly focussed research question	
Description of participant recruitment	
Randomization methods	
Blinding	
Allocation concealment	
Attrition	
Data collection and inclusion/exclusion criteria	
Statistical analysis methods and provision of confidence intervals	
Clearly defined outcomes	
Appropriate outcome assessment instruments	
Adequate controls	
Reporting of study limitations	
Measures taken to control for confounders	

Adapted from the National Health and Medical Research Council levels of evidence guidelines.<sup>18</sup>

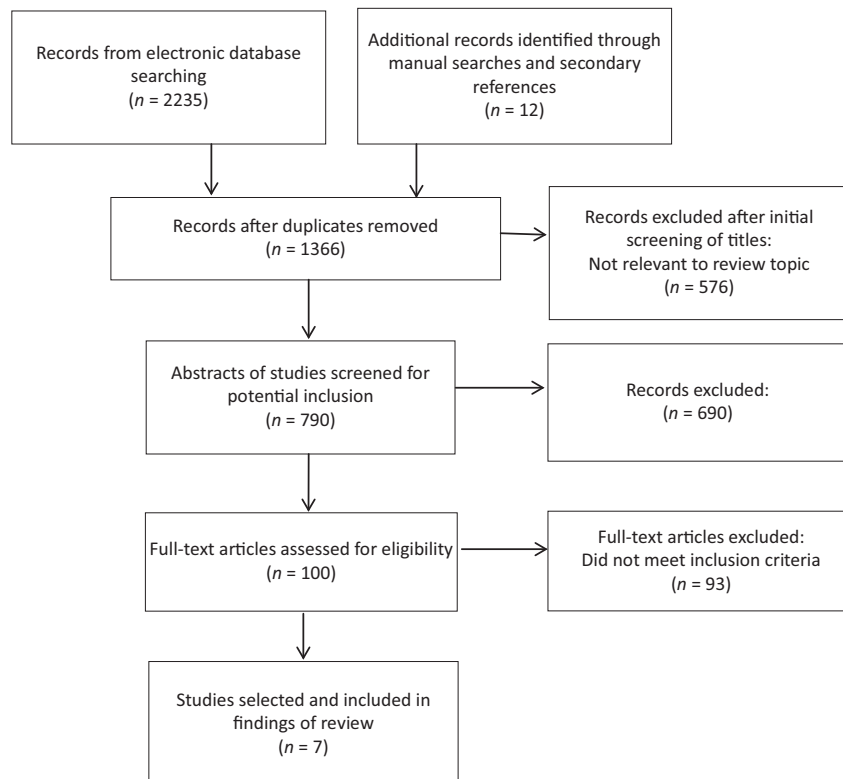
with low risk representing one or no items, medium risk two to three items and high risk being more than three items. In Table 1, an overview of the rating scale items employed for the quality of evidence is provided.<sup>16–18</sup>

## RESULTS

There were 2247 potentially relevant citations retrieved from the searches of electronic databases, journal hand searching and secondary references. After removal of duplicates, preliminary relevance screening of titles identified 790 articles for further evaluation. Abstracts of these articles were reviewed, resulting in the exclusion of 690 publications on the basis of not meeting the required inclusion criteria. The full-text publications were retrieved for the remaining 100 articles. Of these, 93 failed to meet eligibility criteria, leaving seven articles to be included in the review.<sup>9,11,19–23</sup> Figure 1 shows an overview of the article selection review process. Due to the significant variation in interventions, outcome measures and settings, the seven included studies did not allow for a pooled analysis. A narrative approach to the search findings was undertaken instead and a qualitative synthesis of the data is presented here.

### Overview of included studies

Table 2 provides a summary of the included studies. Included study types consisted of two RCT<sup>19,20</sup> and five cluster RCT.<sup>8,11,22–24</sup> Three main categories of NPI were identified among the included studies: (i) disinfection



**Figure 1** Overview of the article selection review process.

**Table 2** Summary of included studies

Study (first author, year, location)	Study type	Sampling	Setting	NPI evaluated	Intervention description	Control	Intervention duration and frequency	Summary of findings on effectiveness	Pandemic or seasonal
Disinfection and hygiene: Abe 2006, Japan <sup>19</sup>	RCT	190 elderly patients visiting day care service	Community	Oral care	Professional oral care consisting of cleaning of teeth and gingivae by dental hygienist in addition to guidance on oral care. (n = 98)	Personal oral care as usual. (n = 92)	Once weekly for a period of 6 months	Study suggested weekly professional oral care and oral health advice reduced the risk of infection from influenza by reducing the number of oral bacteria and neuraminidase and trypsin-like protease activities in saliva.	Seasonal
Satomura, 2005 & supplement; Kitamura 2007, Japan <sup>20,21</sup>	RCT	380 healthy participants at 18 sites across Japan during 2002–2003 winter season.	Community	Gargling	Water gargling group (n = 122) and povidone-iodine gargling group (n = 132).	Usual personal care (n = 130).	60 days. Gargling conducted 3 times a day.	No significant preventive effects were found for gargling and ILI infection. No significant differences were observed between effectiveness of water gargling and povidone-iodine gargling in prevention of ILI.	Seasonal
Barriers: Canini, 2010, France <sup>11</sup>	Cluster RCT	Households from 3 French regions during 2008–2009 influenza season. Index patients selected by GPs. n = 105 households (306 contacts).	Community	Surgical masks	Index patient was required to wear a surgical mask in the household for a period of 5 days from a medical visit when in a shared or confined space. Masks were changed every 3 h and not required to be worn at night, however were encouraged to sleep alone. (n = 52 households/index patients).	Control arm had no intervention applied. (n = 53 households/index patients)	7 days	No significant differences were found between surgical mask use and non-mask use. Low effectiveness is suggested for surgical masks in the prevention of influenza transmission. Fomites and contaminated surfaces are indicated to be a greater proportion of influenza transmission routes than large droplet.	Seasonal
Combined NPIs: disinfection, barriers Aiello, 2010, USA <sup>22</sup>	Cluster RCT	Students from University residence halls recruited during 2006–2007 influenza season (n = 1437).	Community	Hand hygiene, face masks and education	Mask and hand sanitizer group (n = 367). Face mask-only group (n = 378). Both treatment groups received basic hand hygiene education.	Control group received basic hand hygiene education-only (n = 552).	6 weeks duration. Baseline, followed by weekly web-based survey.	Findings suggest that face masks and hand hygiene may reduce spread of respiratory illness in shared living settings and may mitigate pandemic influenza transmission.	Seasonal
Aiello, 2012, USA <sup>23</sup>	Cluster RCT	Students from University residence halls recruited during 2007–2008 influenza season were recruited (n = 1178)	Community	Hand hygiene, face masks and education	Face mask and hand hygiene group (n = 349) and face mask-only group (n = 392). All participants received basic hand hygiene education.	Control group received basic hand hygiene education-only (n = 370).	6 weeks duration. Baseline, followed by weekly web-based surveys.	Face mask and hand hygiene combined were associated with reduced ILI rates and may reduce the spread of influenza in community settings.	Seasonal
Cowling, 2009, China <sup>8</sup>	Cluster RCT	Households in Hong Kong. Index subjects were recruited from 45 outpatient clinics with confirmed influenza. Total of 259 households (794 contacts).	Community	Hand hygiene, face masks and education	Hand hygiene treatment group (n = 85 households) Face mask + hand hygiene treatment group (n = 83 households). Both treatment groups also received education on lifestyle measures.	Control arm received education regarding lifestyle measures (n = 91 households).	6 days duration. Households were visited on days 1, 3 and 6.	No significant difference was found between the face mask plus hand hygiene group and the hand hygiene group in RT-PCR-confirmed influenza virus infections in household contacts.	Seasonal
Larson, 2010, USA <sup>24</sup>	Cluster RCT	Households were recruited from the upper Manhattan neighbourhood with a high population of immigrant Latinos. n = 2788 (509 households).	Community	Hand hygiene, face masks and education	Intervention groups were education and hand sanitizer group (n = 169 households) and education, hand sanitizer and face mask group (n = 166 households).	Education only group (n = 174 households)	Study protocol duration was 19 months. Mean duration was 55.5 weeks.	The wearing of face masks was associated with reduced secondary transmission in households. It is also suggested that alcohol-based hand hygiene may confer protection against influenza transmission in communities. Compliance with face masks was poor.	Seasonal

ILI, influenza-like-illness; RCT, randomized control trials.



and hygiene; (ii) barriers; and (iii) combined NPI: disinfection, hygiene and barriers. The studies were classified into these groups based on the nature of the NPI used or described. All studies involved seasonal influenza in community settings. Study participants were healthy or influenza-infected volunteers and patients from a variety of community sources including aged-care facilities, university residences and households. Frequency and duration of the interventions varied among the studies. Sample sizes ranged from 190 to 2788 and originated from five different countries.

### Types of interventions

Disinfection and hygiene interventions focussed on personal hygienic practices, these including oral care<sup>19</sup> and gargling.<sup>20,21</sup> Barrier interventions included studies on the effectiveness of surgical masks.<sup>11</sup> Combined NPI involved multiple interventions used concurrently with the most common combination being hand hygiene, face masks and education, which was evaluated in four different studies.<sup>8,22–24</sup>

### Quality assessment and evidence level summary

The quality of the influenza NPI studies included in this review was assessed and has been tabulated in Table 3. Of the seven RCT, one study did not report random sequence generation technique.<sup>19</sup> Allocation concealment was not described in four trials.<sup>19,22–24</sup> None of the trials was double blinded. No blinding methods were reported in three trials,<sup>19,20,24</sup> while four trials reported blinding methods for investigators or

acknowledged the impossibility of blinding participants and investigators due to the nature of the intervention (face mask use).<sup>8,11,22,23</sup> Appropriate analysis was used for the five cluster RCT with all studies reporting cluster coefficients.<sup>8,11,22–24</sup> In terms of reliability and assessment of the primary outcome, only one study used laboratory confirmation by reverse-transcription polymerase chain reaction (RT-PCR) as their primary analysis.<sup>8</sup> One study used rapid antigen detection kits,<sup>19</sup> three studies used ILI case definitions as their primary analysis and laboratory confirmed RT-PCR for a fraction of the study groups.<sup>22–24</sup> Two trials used ILI case definitions only.<sup>11,20</sup> Other problems identified were lack of statistical power,<sup>11,19</sup> early termination of the trial<sup>11</sup> and possible confounding in the non-intervention control groups in which an increased awareness of influenza could have led to increased protective measures against influenza infection.<sup>8,11,19,22–24</sup> Furthermore, in cases where interventions were tested in shared living environments such as university dormitory halls, the risk of detection and contamination between study groups was particularly high.<sup>22,23</sup>

### Effectiveness of NPI in preventing and reducing influenza transmission

#### Disinfection and hygiene

Two studies from Japan investigated gargling and oral hygiene as interventions to interrupt transmission. One RCT indicated gargling was effective at decreasing the overall upper respiratory tract infection rates (water gargling incidence rate ratio 0.64, 95%

**Table 3** Quality assessment of included studies

NPI category	Intervention	Total no. studies	Study ID	Risk of bias	Summary of evidence
Disinfection and hygiene	Oral care	1	Abe, 2006 <sup>19</sup>	Med	Suggested effectiveness in prevention of influenza in the elderly.
	Gargling	1	Satomura, 2005 & Kitamura, 2007 <sup>20,21</sup>	Med	No significant protective effects against ILI.
Barriers	Surgical mask	1	Canini 2010 <sup>11</sup>	Low	Low effectiveness against influenza transmission.
Combined NPI	Hand hygiene, face masks and education	4	Aiello, 2010 <sup>22</sup>	Low	Face masks and hand hygiene may reduce spread of influenza in shared living areas.
			Aiello, 2012 <sup>23</sup>	Low	Face masks and hand hygiene appear to reduce rate of influenza in the community.
			Cowling, 2009 <sup>8</sup>	Low	Hand hygiene and face masks seem to prevent household transmission of influenza
			Larson, 2010 <sup>24</sup>	Med	No detectable additional benefit of hand hygiene or face masks in reducing rates of URIs. Mask wearing may reduce secondary transmission.

NPI, non-pharmaceutical intervention.

confidence interval (CI): 0.41–0.99; povidone-iodine incidence rate ratio 0.89, 95% CI: 0.60–1.33); however, there were no benefits found specifically against seasonal ILI infection rates for either intervention.<sup>20,21</sup> The other Japanese RCT investigated the effects of professional oral care by dentists versus standard oral care among elderly participants visiting community day care services. The relative risk of influenza infection for professional compared to standard oral care was 0.1 (95% CI: 0.01–0.81,  $P = 0.008$ ), suggesting professional oral care may confer some protective benefit in the elderly through reduction of bacterial and enzymatic activities in saliva.<sup>19</sup>

### Barriers

In a French cluster-RCT assessing the effectiveness of surgical face masks alone against influenza transmission in community households, no significant differences were noted in the rate of secondary ILI (difference between control and intervention group of 0.40% (95% CI: –10% to 11%,  $P = 1.00$ )).<sup>11</sup>

### Combined NPI

Four cluster RCT tested combinations of education, face masks and hand hygiene, and were assessed within community settings. Two US studies by Aiello *et al.*<sup>22,23</sup> were carried out in university halls during two consecutive influenza seasons (2006–2007 and 2007–2008). Results for one of these trials found cumulative reductions in influenza rates for both face mask with hand hygiene group (43%, adjusted relative risk (RR) = 0.57 (95% CI: 0.26 to 1.24)) and face mask-only group (8%, adjusted RR = 0.92 (95% CI: 0.59 to 1.42)) compared to the control; however, statistical significance was not attained.<sup>23</sup> Similarly, the other trial observed a ~10% reduction in cumulative ILI incidence for both face mask with hand hygiene and face mask alone compared to the control group yet did not reach statistical significance.<sup>22</sup> A study by Cowling *et al.*<sup>8</sup> conducted in Hong Kong households involved laboratory-confirmed influenza index patients. This study found that hand hygiene (with or without face masks) appeared to reduce influenza infection, although differences were again not statistically significant compared to control. Comparably, the trial by Larson *et al.*<sup>24</sup> conducted in USA households showed that the hand hygiene-only group had a higher protective effect against developing influenza symptoms (57.6%,  $P < 0.01$ ), compared to the hand hygiene with face mask group (38.7%) and control group (49.4%); however, no significant differences were found in infection rates by intervention groups,<sup>24</sup> suggesting hand hygiene may have some general protective effect. Common issues in all studies were that the protective effects of each individual intervention were difficult to discern, with adherence of face mask use in particular being poorly described indicating an inability to demonstrate significant change due to small numbers in studies or a lot of noise in measurements or both.

### Awareness and education on NPI

Five studies included some form of educational component related to either the appropriate use of NPI or

influenza viral transmission as part of the intervention or control group.<sup>8,11,22–24</sup> These studies utilized education, guidance or advice as part of a comprehensive layered NPI approach, and were associated in each case with increased influenza awareness and contributed to the overall intervention effect.

### Excluded studies

Among the excluded articles, 19 were identified as not being RCT, however met other inclusion criteria.<sup>5,25–42</sup> The level of evidence types consisted of seven level III-2 studies (prospective/retrospective cohort, case control and quasi-experimental) with the remaining studies being level III-3 (retrospective cross-sectional, cross-sectional, historical observational). The overall quality of these excluded studies was poor, with only a small number representing a low risk of bias. Of the 19 studies, 11 were quarantine, surveillance or social distancing interventions; three were disinfection and hygiene studies, three assessed combined NPI, and two studies evaluated barrier interventions. Twelve of the 19 studies were conducted during pandemic conditions, six during seasonal influenza and one study during both seasonal and pandemic influenza conditions. Settings comprised community (eight studies), health care (nine studies) and international airports (two studies).

Of the few excluded studies that were evidence level III-2 and had the least methodological issues, there were promising results in one study assessing the use of hand hygiene and education.<sup>26</sup> In this study, a higher frequency of hand washing after contact with contaminated surfaces was found to be a protective factor against influenza hospitalization. Also, and importantly, receiving less information on influenza pandemic precautions was associated with likelihood of influenza infection.<sup>26</sup> Among the evidence level III-3 excluded studies with low risk of bias, five studies reported effectiveness for NPI. These interventions included protective sequestration measures for at-risk populations,<sup>5</sup> school closure,<sup>35,39</sup> entry screening<sup>37</sup> and open-air treatment.<sup>40</sup>

## DISCUSSION

The evidence for NPI reducing influenza viral transmission during seasonal and pandemic outbreaks was lacking with most studies being significantly flawed. There were only a few studies with acceptable methodological quality, and of these very few showed statistically significant differences. The key NPI reported in the well-designed studies were related to disinfection, physical barriers such as face masks, multifaceted interventions that combined disinfection, hygiene and barriers and studies associated with population based barriers such as quarantine and social distancing and surveillance.<sup>8,19,22–24</sup> In the acute care clinical setting, a comparison of N95 respirator and surgical masks found neither mask to be superior in protecting health professionals against influenza.<sup>43</sup>

Simple and yet potentially effective measures for disinfection included oral hygiene and hand washing

to reduce transmission. These low-cost infection control methods were likely to be effective given that influenza virus has been found to survive for up to 30 min on unwashed hands.<sup>44</sup> There is evidence for hand washing with water alone being as effective in removing colony forming units and viruses compared to disinfectant.<sup>45</sup> The effectiveness of oral hygiene may be due to reducing the oral load of influenza virus and thereby minimizing systemic influenza infection especially in the elderly.<sup>19</sup>

Health professionals are at risk of becoming infected when delivering clinical care to influenza infected patients and physical barriers such as surgical masks and N95 respirators<sup>11</sup> have been proven to be effective in acute settings. Using these personal physical barriers in the community is without evidence and does not seem to reduce influenza symptoms or rates of influenza. The combination of disinfection and barrier methods has been purported to reduce secondary influenza infection in people who live in university residential accommodation.<sup>22,23</sup> However, it is not known if the students' behaviour changed including reduced socialization due to the reporting of influenza deaths in the media. Despite several complex interventions being studied, hand hygiene is likely to be the most effective in reducing rates of influenza transmission, but this is based on very limited data.

Quarantine measures have been considered standard practice as part of infection control in human and animal migration.<sup>46</sup> Quarantine measures for influenza usually consist of infected individuals remaining at home until they are no longer infectious. However, there is data to suggest that this measure is acceptable to people with influenza<sup>47</sup> while home-based quarantine raises a number of other issues relating to safety, education and information<sup>48</sup> and the availability of sick leave and other financial support mechanisms.<sup>49</sup> Nevertheless, compliance with home quarantine has been reported as being high. Our findings build considerably on a previous review<sup>10</sup> which was limited to assessing physical barriers and provides the additional finding of the potential for oral care in reducing transmission of the influenza virus while confirming the ongoing need for methodologically sound and well-designed studies.

In conclusion, this review found a small number of NPI appeared to be useful in reducing the transmission of influenza, with oral hygiene and hand washing showing efficacy. The implementation of home quarantine may be useful but requires further assessment. Overwhelmingly evident was the need for well-developed and carefully planned large-scale studies to assess the efficacy of NPI and to address the important question of whether we can limit influenza spread using NPI methods.

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### Supplementary Information

Additional Supplementary Information can be accessed via the *html* version of this article at the publisher's web-site.

**Table S1** Search strategy for Medline OvidSP.

**Table S2** Topically relevant excluded studies.