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Review

Do we have enough evidence how seasonal influenza is transmitted and can be prevented in hospitals to implement a comprehensive policy?

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ABSTRACT

Purpose: To identify if there is enough evidence at low risk-of-bias to prevent influenza transmission by vaccinating health-care workers (HCWs), patients and visitors; screening for laboratory-proven influenza all entering hospitals; screening asymptomatic individuals; identifying influenza supershedders; hand-washing and mask-wearing by HCWs, patients and visitors; and cleaning hospital rooms and equipment.
Principal Results: Vaccination reduces influenza episodes of vaccinated (4.81/100 HCW) compared to unvaccinated (7.54/100) HCWs/influenza season. A Cochrane review found for inactivated vaccines the Number Needed to Vaccinate (NNV) = 71 (95%CI 64%, 80%) for adults 18–60 (same age as HCWs) to prevent laboratory-proven influenza. There are no RCTs of screening HCWs, patients, visitors and influenza supershedders to prevent transmission. None of four RCTs of HCWs mask-wearing (two directly observed, two not) showed an effect because they were underpowered either due to small size or low circulation of influenza. Hospital rooms and equipment can effectively be cleaned of influenza by many chemicals and hydrogen peroxide vapor machines but the cleaning cycle needs shortening to increase the likelihood of adoption.
Major Conclusions: HCW vaccination is a partial solution with current vaccination levels. There are no RCTs of screening HCWs, patients and visitors demonstrating preventing influenza transmission. Only one study costed furloughing HCWs with influenza and no RCTs have identified benefits of isolating influenza supershedders. RCTs of directly- and electronically continuously-observed mask-wearing and hand-hygiene and RCTs of incentives for meticulous hygiene are required. RCTs of engineering solutions (external venting, frequent room air changes) are needed. A wide range of chemicals effectively cleans hospital rooms and equipment from influenza. Hydrogen peroxide vapor is effective against influenza and a wide range of bacterial pathogens with patient room changes, and clean areas cleaners do not clean but its cleaning cycle needs shortening to increase the likelihood of adoption of cleaning rooms vacated by influenza patients.

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1. Introduction

1.1. Objectives

To identify whether there is a chain of evidence at low risk-of bias that influenza transmission can be prevented in hospitals by vaccinating health-care workers (HCWs), patients and visitors; screening for acute respiratory illnesses all entering hospitals and determining with rapid tests which ILI cases have laboratory-proven influenza; screening asymptomatic individuals for influenza; identifying influenza supershedders; hand-washing and mask-wearing by HCWs, patients and visitors to prevent transmission by droplets, aerosols and fomites; and cleaning hospital rooms and equipment.

Background: There is a substantial burden of influenza in hospitals during influenza seasons. The Canadian national hospitalization database 1994/5 to 1999/2000 estimated the annual influenza hospitalization rate of those ≥20 years was 65/100,000. For those ≥65 it was 27–340/100,000, and their rates were 30–110/100,000 for RSV, 60–90/100,000 for parainfluenza and 130–350/100,000 for other viruses. The period included three severe influenza seasons [1]. However, an Argentinian study

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2002–9 found lower excess hospitalization rates for pneumonia and influenza combined during influenza seasons of 20/1000,000 [2].

A study using US Medicare data 1987–99 found that annual admissions for pneumonia and influenza increased from 15.1 to 23.4/1000; 23% of this increase was due to population ageing, 2.4% to rehospitalization and 5% to upcoding but there was no evidence physicians were admitting less complicated cases to explain the remaining increase [3]. A prospective surveillance study of laboratory-confirmed influenza in the Canadian Nosocomial Infection Surveillance Program 2006–12 (a nosocomial infection was defined as symptom onset >96 h after admission) and identified 3299 influenza nosocomial infections. Of these 570 (17.23%) were healthcare associated (39.5% in an acute care and 60.5% in a long-term care facility) [4]. Thus influenza rates in hospitals are of concern.

2. Materials and methods

Medline was searched from inception to 15 April 2016 using the search terms: (1) Nurses or Physicians or doctor.mp or healthcare aide.mp or health care worker.mp or Health Personnel or Allied Health Personnel), (2) Hospitals, (3) influenza, Human, (4) (disease transmission.mp, infection or Infection Control or Disease Transmission, Infectious, or Communicable Diseases or infectious disease transmission.mp or professional to patient.mp), (5) (vaccination or immunization), (6) (Hand Hygiene or Hand Disinfection or handwashing.mp), (7) Masks or Respiratory Devices or N95 respirator.mp). Separate searches were then conducted for each search for (8) (randomized controlled trial or randomized controlled trial) or (9) (meta-analysis or systematic review.mp). Embase and Cochrane Central were searched using similar terms.

3. Results

Medline was searched from inception to 15 April 2016 using the search terms: (1) Nurses or Physicians or doctor.mp or healthcare aide.mp or health care worker.mp or Health Personnel or Allied Health Personnel) = 451328 citations; then (2) Hospitals + (3) influenza = 215 citations; (1) + (2) + (4) Human and (disease transmission.mp, infection or Infection Control or Disease Transmission, Infectious, or Communicable Diseases or infectious disease transmission.mp or professional to patient.mp) = 1828 citations; (1) + (2) + (3) + (5) (vaccination or immunization) = 121 citations; (1) + (2) + (3) + (6) (Hand Hygiene or Hand Disinfection or handwashing.mp) = 2 citations, and (1) + (2) + (3) + (7) Masks or Respiratory Devices or N95 respirator.mp) = 7 citations. Separate searches were then conducted for each search for (8) (randomized controlled trial or randomized controlled trial) or (9) (meta-analysis or systematic review.mp). Embase was searched with similar results and Cochrane Central was also searched using similar terms. Additional studies were identified from article reference lists and 54 citations were retained for this review.

3.1. Transmission of influenza

A systematic review of studies of influenza transmission in humans and animals concluded that transmission occurs mostly at close range (less than 1 metre) by contact or droplets and less by aerosols at greater distances [5].

The key period of influenza shedding is the two days after symptom onset. A systematic review of 56 studies of health volunteers (n = 1280) who accepted infection with influenza A found viral shedding increased sharply from half to a day after symptoms onset, peaked at 2 days, with total shedding duration 4.8 days (95%CI 4.31, 5.29) [6].

About 50% of particles 4–6 μm can be deposited in the alveoli but particles >10 μm are not respired in the alveolar region (and contain 99% of the aerosol volume and presumably RNA virions). Large droplets from a cough or sneeze usually travel <60 cm and need to be directed at the person, and fine particles can remain suspended for many minutes. Transmission from fomites is increased if influenza is repeatedly deposited or deposited with body fluids such as nasal mucous or there is repeated contact with HCW hands or frequent self-contact (unobserved nose picking and eye rubbing often occur > twice hourly) [7].

An important question is how many patients provide transmissible viable influenza. A study of 47 students RT-PCR positive for influenza found 81% had influenza viral RNA in their cough aerosols with 65% in particles <4 μm, which remain airborne for an extended time and can be inhaled into alveoli. There were large variations in virus numbers in the cough aerosols, with four subjects providing 45% of total influenza viral RNA. Eleven of 30 subjects had viable virus (6.0×10^4 pfu/ml; SD 2.85×10^5) on plaque assays from nasopharyngeal swabs [8].

Several studies have shown wide variation in the viral load expelled by patients. A study of nine influenza patients found they coughed an average of 75,400 particles/cough (range 900 to 308,600) and an average 2.48 l air/cough (range 1.08, 6.95 L). After recovery they still expelled 52,200 particles/cough (range 1100 to 308,600) [9].

A study evaluated influenza shedding by 61 patients in a North Carolina hospital in rooms with 6 air changes/hour, at 20 °C, relative humidity 40% and end filters compliant with American National Standards Institute standard 52.2–2007. A foot from the patient's head 300 RNA copies >4.7 μm and 100 RNA copies ≤4.7 μm were detected, with the opposite particle size distribution six feet from the patient's head (5 RNA copies >4.7 μm and 80 RNA copies ≤4.7 μm). The five highest emitters shed 32 more times virus (up to 20,400 RNA copies per 20 min) compared to the other emitters (<1300 RNA copies) [10].

Supershedders were also identified in a Hong Kong study. Twenty per cent of the most infectious children with influenza were responsible for 96% of total viral shedding by children (average influenza viruses shed/infection = 9 million (range 20th to 80th percentile = 800,000 to 100,000,000), and 20% of the most infectious adults were responsible for 82% of the total adult viral shedding (average shed/infection = 20,000,000 (range 20th to 80th percentile = 4,000,000 to 90,000,000) [11].

A study of cough etiquette asked 31 healthy non-smokers to cough while covering their mouth and nose with their hands, sleeve/arm, tissue or a surgical mask. The explosive force of coughing and sneezing has to escape somewhere and laser beams showed the manoeuvres merely redirected the cough plume [12]. Droplet numbers would be much higher in influenza.

Studies of influenza transmission often do not control for confounders such as the vaccination status and handwashing of HCWs and patients, numbers of infected HCWs and patients, supershedders, numbers of procedures, amount of coughing and virus exhaled, surfaces and care items contaminated, length of stay, ward layout and ventilation, and there are no RCTs which controlled all these factors.

3.2. Does vaccination of health-care workers prevent influenza in HCW?

Most HCWs are 18–60 years old, and a Cochrane review of vaccinating healthy adults 18–60 against influenza provides appropriate data for this age group. The review identified 48 RCTs and 21 clinical trials (n > 70,000), 27 cohort studies (≈8 million), and

20 case–control studies (≈25,000)]. NNV to prevent one case of laboratory-proven influenza for inactivated vaccines was 71 (95%CI 64%, 80%), and for one- or two-dose whole-virion pandemic vaccines 35 (33%, 47%) [13]. A systemic review used a smaller data base (17 RCTs and 14 observational studies) and concluded that in adults 18–65 trivalent inactivated vaccine was effective (RT-PCR or culture) in 8 of 12 seasons with a pooled efficacy of 59% (95%CI 51, 67) and there was no evidence for efficacy in adults ≥65 [14]. Another systematic review compared 29 surveys (n = 58,245) during 97 influenza seasons of influenza infection rates in HCWs and healthy adults 18–60 and concluded infection rates were higher in HCWs. Serological studies (four-fold increase in antibody titre) found 3 (1.79, 5.15) symptomatic influenza infections/influenza season/100 vaccinated working adults and 5.12 (3.08, 8.52) for unvaccinated working adults and 4.81 (3.23, 7.16) for vaccinated HCW workers and 7.54 (4.86, 11.70) for unvaccinated HCWs and households with children had higher rates of influenza [15]. The limited number of studies of culture or PCR found larger differences between vaccinated and unvaccinated individuals. Self-selection for vaccination could not be assessed. Vaccination thus reduces the risk of influenza by <50% in HCWs compared to not being vaccinated but is not a complete solution.

3.3. What percentage of hospital HCWs receive influenza vaccination, and what factors tend to increase these rates?

A systematic review identified 22 studies in hospitals in eight countries which used an intervention to increase HCW vaccination rates and compared them either with rates in a previous season or with another intervention. The median baseline vaccination rate was 29%, the median increase 17%, and the four multi-year (2–5 years) studies from a baseline of 54% achieved final rates ranging from 78 to 99%. Two long-term studies (12 and 18 years) from low baselines of 4% and 25% eventually reached a 2/3 vaccination rate. Programs used differing combinations of strategies (free readily available vaccine, dedicated personnel, extensive communication, active refusal, strong and visible leadership, long-term implementation) and the authors concluded that mandatory vaccination programs were the most effective [16]. Another systematic review identified seven studies in hospitals but only found two RCTs and only one found a small significant increase in vaccination rates in the study arm that received a letter from the chief of infectious diseases [17].

A Centers for Disease Control (CDC) Internet panel survey in 2012 of US healthcare workers found that of 2348 HCW 85.6% of physicians, 77.9% of nurses, and 62.8% of other HCWs were vaccinated, and 76.9% of all HCWs in hospitals, 67.7% in physician offices, and 52.4% in long-term care facilities (LTCFs). In hospitals requiring influenza vaccination 95.2% were vaccinated and 68.2% in hospitals not requiring vaccination [18]. A study of 3275 HCWs in a Canadian tertiary care hospital found that the strongest predictors of influenza vaccination were a desire to protect family members and patients, believing vaccination is important even if one is healthy, confidence in vaccine safety and no adverse effects, and supervisor and physician encouragement [19]. A study of 7279 HCWs in the St Louis area obtained a 43.8% response rate and reported 78.9% were vaccinated in the 2010/2011 seasonal vaccine and 63.3% for H1N1. Vaccination rates were not reported for the 1506 hospital HCWs but 51% reported their employer had a mandatory vaccination policy but of these 64% said it was not enforced [20]. The most effective mandatory vaccination program is the Washington University Hospitals group in St. Louis, USA, with 25,561 (98.4%) of 25,980 active employees vaccinated. Those neither vaccinated nor exempted were initially suspended without pay and then dismissed. However, most attending physicians were either affiliated with the university or in private practice and were not covered by this policy and their vaccination rates were not reported [21]. Thus HCW vaccination rates are lower than the US Department of Health and Human Services goal of 90% by 2020 [22], the results of vaccination campaigns vary widely by country and institution, and there has been no RCT of transmission with high (90%) HCW influenza vaccination rates.

3.4. Does HCW influenza vaccination reduce influenza rates in patients?

A systematic review of HCW vaccination identified only three RCTs [23], and only one reported laboratory-proven influenza with VE 88% (59%, 96%), p = 0.0005 [24]. Despite the importance of the topic there is no other RCT with the outcome of laboratory-proven influenza.

The only other studies of potential transmission of influenza by HCWs to patients are in nursing homes. A Cochrane review of whether vaccinating HCWs prevents influenza in elderly patients they care for in nursing homes identified only three RCTs [25]. No conclusions could be drawn due to performance bias (insufficient staff vaccination), detection bias (insufficient sampling to detect patient influenza) and no study reported staff influenza [26–28]. Nursing home patients are older, have more co-morbidities and much longer stays than hospital patients and it is uncertain whether their results would predict hospital experience. A study in the largest hospital in Brazil during the 2009 H1N1 pandemic assessed staff for ILI and furloughed 3% but did not assess the effect on patient influenza rates [29]. There are no studies comparing screening patients and their visitors for influenza, or of transmission of influenza by vaccinated or unvaccinated visitors to other patients or HCWs.

3.5. Asymptomatic influenza carriers

A systematic review of laboratory-proven influenza found for 11 studies of influenza outbreaks (10 Real-Time Polymerase Chain Reaction [RT-PCR], 1 culture) the pooled mean of asymptomatic cases was 16% (95%CI 13%, 19%) with low heterogeneity (I^2 = 0%), and for 19 studies (paired sera) in which individuals were followed during entire epidemics most point estimates were that asymptomatic individuals were 65–85% of the total with high heterogeneity (I^2 = 97%) [30]. [N.B. RT-PCR amplifies DNA products reverse transcribed from mRNA to study gene expressions with low abundance]. There have been no studies testing HCWs, patients and visitors during influenza seasons with rapid flu tests to identify symptomatic and asymptomatic infected individuals.

3.6. Facemask wearing and handwashing by health-care workers

Influenza lasts longest on stainless steel (up to 24 h) and for much shorter times on porous surfaces. There is minimal decrease in titre immediately after transmission to hands but a rapid decrease by 15 min [31–35]. In a study of 18 HCWs at the University of North Carolina Hospital who wore scrub suits, a contact isolation gown, N95 respirator, eye protection, and two pairs of latex gloves, 5 sites on the outfits were contaminated with 5 $\log_{10}$ PFUs MS2 bacteriophage. During equipment removal the virus was transferred to hands in 14/18 of the single-glove and 5/18 of the double-glove trials (p = 0.006), and to the inner glove in 17/18 of the double-glove trials. The commonest errors leading to higher contamination were touching the respirator and eye protection on the front rather than on the straps and pulling the gown off by the sleeves instead of the neckline (p < 0.0001) [36].

A key issue is whether HCWs actually wash their hands for each five World Health Organization (WHO) patient-contact moments (Before patient contact, Before aseptic task, After body fluid

Table 1
RCTs of the effectiveness of HCW mask wearing and hand hygiene to prevent transmission of influenza.

Author, date country	Participants and intervention	Study design	Comparison	Influenza rate in community, vaccination status of participants	Outcome	Compliance with mask wearing	Results
Health care workers, mask wearing directly observed, outcome = laboratory confirmed influenza in HCW							
Loeb 2009, Canada [38]	Emergency departments, medical and pediatric units in 8 Ontario tertiary care hospitals during 2008/9 influenza season. When caring for febrile respiratory patients during influenza season: (1) 225 nurses randomized to surgical masks, and (2) 221 fit-tested N95 respirators. [It was routine practice to wear gowns and gloves in room of patient with febrile respiratory illness); no data on training or fit testing (although fit testing of masks was compulsory for nurses in Ontario]	C-RCT; randomization by independent clinical trials coordinating group; lab staff conducting influenza tests blinded; 225 randomized to surgical mask (212 included in analysis); 221 randomized to N95 (210 included in analysis)	No control	"Largely unvaccinated cohort of nurses followed closely during a period of relatively mild influenza-like illness and into the beginning of what is now considered a pandemic period" [H1N1 pandemic]. Vaccinated against influenza: 30.2% surgical mask group, 28.1% N95 respirator group	Web based self-report of influenza signs and symptoms weekly (those who did not report were contacted) and those with new symptoms performed nasal swab; Influenza by RT-PCR or 4 fold rise in serum titres	Research assistant called medical and pediatric units to ask if any patients admitted with droplet precautions for influenza or febrile respiratory illness; "a trained auditor was sent to the unit to observe for compliance. The auditor was instructed to stand a short distance from the patient isolation room . . .to accurately record the audit." Only 1 room entry reported per observation. No audits within patient rooms or emergency department, no audit of hand hygiene or use of gloves or gowns.	**Influenza by RT-PCR or 4 fold rise in serum titres (per protocol not intention-to-treat analysis):** 23.6% mask, 22.9% N95; RD = -0.73% (95%CI -8.8%, 7.3%), $p = 0.86$ **Attrition:** [212/225 surgical mask and 210/221 N95 analyzed] Macintyre 2013 argues was "probably underpowered"; "care was "only during care of identified febrile patients with ILI or having high-risk procedures;" and "the study does not disclose the serologic status of those participants who received influenza vaccination, who seem to have been included in the denominator for analysis."
MacIntyre 2011, China [39]	Beijing emergency departments and respiratory wards (high risk for respiratory exposure) in 15 hospitals (5 Level 2, 10 Level 3 with more sophisticated equipment) for respiratory outbreaks during study period Dec 2008 to Jan 2009; participants wore masks or N95 every shift x 4 weeks; (1) surgical masks (492 HCWs in 5 hospitals); (2) N95 fit-tested 461 HCWs in 5 hospitals; (3) N95 not fit-tested 488 HCWs in 5 hospitals; staff instructed on hand hygiene putting on and removing masks	C-RCT, hospitals computer randomized; power computation for 5% attack rate N95 arm (fit tested), N95 arm (not fit tested) and 12% medical mask arm, 80% power, alpha = 5%, intra cluster correlation 0.01 required 500/arm	Non-random sample emergency departments and hospital wards in 9 hospitals of HCWs who did not wear masks (randomized control group not acceptable to Chinese ethics board as mask wearing was widespread)	All hospitals monitored for respiratory outbreaks during study period Dec 2008 to Jan 2009 and none detected; participants contacted daily or face-to-face identify cases of respiratory infection and head nurse on each ward followed up reports and identified illness; District CDC also monitored sites daily.	Laboratory confirmed Influenza RT-PCR; given thermometer to record daily temperature or if symptoms; self reported ILI on daily diary cards monitored weekly by researchers, self-reported CRI	Not stated how reports of compliance by supervisors and daily diary cards integrated. **Mask wearing during 80% of working days:** N95 fit-tested 74%; N95 non fit-tested 68%, medical mask 76%. Duration of mask wearing: N95 fit-tested 5.2 hours; N95 non fit-tested 4.9 h, medical mask 5 h.	**Intention-to treat multivariate analysis laboratory RT-PCR confirmed influenza:** fit-tested N95 mask 3/461 OR = 0.64 (0.15, 2.68), $p = 0.54$; non fit-tested N95 0/488; surgical mask 5/492. **Intention-to treat multivariate analysis any laboratory confirmed respiratory virus:** fit-tested N95 mask 8/461 OR = 0.69 (0.24, 2.03), $p = 0.50$; non fit-tested N95 5/488 OR = 0.39 (0.12, 1.22, $p = 0.11$; surgical mask 13/492. Study underpowered Mask group included only level 3 (most sophisticated) hospitals; Authors suggest "study may have been underpowered because attack rates were lower than expected."

Table 1 (*Continued*)

Author, date country	Participants and intervention	Study design	Comparison	Influenza rate in community, vaccination status of participants	Outcome	Compliance with mask wearing	Results
Health care workers, mask wearing, not directly observed, outcome = laboratory confirmed influenza							
Jacobs 2009, Japan [54]	17 HCWs wore surgical mask on duty		15 only if task required		Self-reported "cold" symptoms, no lab tests	84% self report	**"cold symptoms"** No significant differences. Study underpowered
MacIntyre 2013, Beijing [55]	Beijing, medical staff on 68 wards in 19 hospitals. (1) medical masks at all times on shift ($n = 592$), or (2) N95 respirators at all times on shift ($n = 581$) or (3) N95 respirators only when doing high risk procedures ($n = 516$)	C-RCT (by ward); observed for 4 weeks of intervention and 4 weeks thereafter to monitor for infections incubated in the first 4 weeks; power computation to detect significant difference between arms: 80% power, two sided 5%, assumed clinical respiratory rate 3.9% in N95 and 9.2% in mask arms, ICC = 0.027, needed 560/arm; intention-to-treat	No control	28 Dec 2009 to 7 Feb 2010 (winter season); staff vaccination rate A(H1N1)pdm09 2009–10 mask (19.1%), targeted N95 (25.2%), N95 (29.4%); p <0.001); Seasonal influenza 2009–10 mask (15.4%), targeted N95 (9.9%), N95 (14.6%); $p = 0.017$); Reported hand washing after patient contact at all times –mask (72.9%), targeted N95 (60.7%), N95 (77.1%); $p = 0.0001$)	1. Laboratory-confirmed Influenza, adenoviruses, human metapneumovirus, coronavirus, parainfluenza 1,2,3, RSV A and B, rhinoviruses A/B 2. ILI (T 38 °C + one respiratory symptom) 3. Clinical respiratory illness (2 respiratory or 1 respiratory and 1 systemic symptom)	Self-report (thermometer; diary cards collected daily), contacted daily to identify respiratory infections; "significantly poorer adherence in the continuous use N95 arm."	**Intention-to-treat laboratory-confirmed respiratory viruses:** mask (19/572, 3.3%), targeted N95 (17/516, 3.3%), N95 (13/581, 2.2%), [Targeted N95 vs. mask $p = 0.985$; N95 vs mask $p = 0.44$] Study underpowered **ILI:** mask (4/572, 3/3%), targeted N95 (2/516, 3.3%), N95 (6/581, 2.2%), [Targeted N95 vs. mask $p = 0.49$; N95 vs mask $p = 0.54$] [6 cases of influenza A or B; other respiratory viruses in 43 staff (of which 17 RSV)] **Intention-to-treat laboratory confirmed bacteria in HCWs with clinical respiratory illness:** medical mask 84/572 (14.7%); targeted N95 52/516 (10.1%); N95 36/581 (6.2% ($p = 0.012$)
MacIntyre 2015, Vietnam	1607 HCWs on 74 high risk wards (emergency, infectious/respiratory disease, ICU, paediatrics)	HCWs randomized to medical masks, cloth mask or control (usually masks) every shift x 4 consecutive weeks		"Circulating influenza and RSV were almost completely absent during this study;" HCW influenza vaccination rates 3%	Laboratory confirmed for 17 viruses; compliance with mask wearing ≥70% of work shift hours		**Intention-to-treat laboratory confirmed viruses in HCWs:** cloth masks 31/569 (5.4%), control 18/458, (4.0%), medical masks 19/580 (3%); (no Influenza A, one Influenza B/rhinovirus co-infection)
Atrie 2011, Canada	221 nurses in emergency, medical and pediatric wards assigned to wear N95 respirators, 225 surgical masks	Randomization centrally, investigators and lab personnel blinded. Noninferiority trials of N95 respirators vs. surgical masks, no control group. Investigators specified lower limit of 95%CI for N95 respirators as 9% lower than for incidence if in HCWs surgical masks	No control	No data on HCW vaccination rates or community rates or HCW influenza exposure in non-clinical settings	Incidence of influenza in HCW, assessed by PCR or fourfold rise in hemagglutinin titres	No data on mask wearing	No significant difference in influenza infection surgical masks 23.6%, N95 respirators 22.9%, $p = 0.86$

HCW: health care worker; ILI: influenza like illness; CRI: clinically reported illness .

exposure risk, After patient contact, and After contact with patient surroundings) [37]. There are two C-RCTs of directly-observed HCW mask wearing (38, 39) comparing surgical masks and N95 respirators without control groups; one (38) was conducted during an H1N1 pandemic and one (39) during a period when the hospital experienced no outbreaks. There are four C-RCTs with mask wearing not directly-observed: two of surgical masks vs. respirators without a control group, one of surgical masks vs. control and one of cloth masks vs. control [40–43]. All the studies were underpowered either because of small numbers or low circulating influenza virus during the study periods and none demonstrated reductions in HCW influenza measured by RT-PCR or culture. One study stated that self-reported handwashing after patient contact took place "at all times" in 72.9% of the group wearing masks, 60.7% wearing N95 respirators only for high risk situations and 77% in the other N95 respirator group and this is the only study reporting hand washing [42]. The same study showed a significant reduction in bacterial carriage in the N95 group [42] (Table 1). There is a small study of nine patients coughing while wearing a N95 respirator, or a surgical mask or no mask and only in the no-mask group were coughs positive for influenza by RT-PCR [44].

3.7. Employees working when ill

There are two national surveys which show high rates of working when ill, and rates are higher in health care. A Swedish telephone survey of 3801 employed individuals 1997 (response rate was 87%) reported one third had worked two or more times during the preceding year although they thought they should have been on sick leave, with higher rates among nurses, nursing aides and teachers [45]. A study of a random sample of 12,935 Danish workers found more than 70% worked at least once annually when ill, with higher rates if the individual was a supervisor, had a close relationship with colleagues, worked more than 45 h/week, was over-committed to work and had conservative attitudes to being absent [46]. There are no studies of screening HCWs with rapid flu tests during respiratory virus seasons to assess the effect on the transmission of influenza to other HCWs and patients.

3.8. Cleaning hospital rooms and equipment

Could improving hospital cleaning decrease influenza transmission rates? Influenza can last for several hours on stainless steel surfaces, but usually for less than 15 min on porous surfaces and hands unless the influenza is deposited in secretions such as sputum. HCW hands, clothing and equipment are reinfected by contact with new influenza deposits on surfaces and by coughing, which they may then transfer to the next patient. H1N1 on stainless steel objects is 99% inactivated after 2.5 min by hydrogen peroxide vapour at 10-ppm, and by triethylene glycol vapour at 2-ppm by 1.3 $\log_{10}$ reductions/hour (16 times faster than natural inactivation rate) [47]. A wide range of surface cleaners are effective against influenza [48,49]. A systematic review found hydrogen peroxide effective against multiple pathogens including MRSA and *C. difficile* [50]. A 500 bed teaching hospital in New Haven decontaminated 1565 rooms with hydrogen peroxide over a 22 month period, of which 1095 rooms had been vacated by patients with *C. difficile*, 219 multidrug-resistant organisms, 110 norovirus and 78 MRSA. However, cleaning took 3–3.5 h compared to 32 min for usual hand-cleaning by bleach. The additional time is the final stage which reduces hydrogen peroxide to <2 ppm by drawing room vapor over heavy metals [51]. The most soiled areas in a hospital room are bedrails and table, floors, toilet floors, window shelves, lockers, grilles and medical equipment including BP and oxygen sensors, ECG machines and defibrillators [52]. Hydrogen peroxide can reach all these surfaces which might be neglected by a cleaner. After cleaners use cloths to remove surface soil, significant amounts of bacteria and spores are transferred from their cloths to the three next consecutive surfaces unless they use a new cloth for each surface [53]. Thus hydrogen peroxide cleaning removes contamination produced by the cleaners. If the time taken by hydrogen peroxide cleaning could be considerably shortened it could be assessed for use especially during influenza pandemics.

4. Discussion

This review updates previous systematic reviews with no limitation of date or language. The largest evidence base is vaccination, which shows 4.81/100 vaccinated HCWs/influenza season will nevertheless have an episode of laboratory-proven influenza compared to 7.54/100 unvaccinated HCWs [15]. There are no RCTs of testing HCWs before shifts for influenza and furloughing them.

There is an extensive literature on the relative spread of influenza by cough droplets, aerosols and fomites, concluding all are potential vectors, but few studies of engineering solutions (frequent room air changes and room external venting).

The key problem with the literature on hand-washing and mask-wearing by HCWs and community resident is few are directly-observed are none are continuously-observed, so there is no true test of the interventions. Neither the two RCTs of the partly directly-observed nor the four RCTs of unobserved HCW mask-wearing showed an effect on influenza transmission.

The literature on cleaning surfaces shows influenza can be effectively removed with correct chemicals and techniques, and that hydrogen peroxide vapour decontaminates surfaces cleaners do not.

5. Conclusions

Vaccination: Vaccination the number of episodes of influenza/100 HCW but is a partial solution with current vaccination levels. There are several uncertainties in the vaccination literature which need resolution. Firstly, because of the uncertainty whether herd immunity could be achieved with higher levels, compulsory vaccination/mask wearing is disputed. A Cochrane review of vaccinating healthy adults age 18–60 found the NNV currently to prevent one case of laboratory-proven influenza for inactivated vaccines is 71 (95%CI 64%, 80%) [13]. Secondly, the Cochrane review of HCW vaccination identified only three RCTs [23] and for the one which reported laboratory-proven influenza the VE was 88% (95%CI 59–96), $p = 0.0005$ [24]. Thirdly, the Cochrane review of vaccinating HCWs to prevent influenza in elderly patients they care for in nursing homes identified only three RCTs and no conclusions could be drawn due to performance and detection bias [25]. Fourthly, vaccinated workers still get influenza: a systematic review found 4.81 (3.23 to 7.16) influenza infections (as measured by a four-fold increase in antibody titre)/100 vaccinated and 7.54 (4.86 to 11.70) unvaccinated HCWs [15]. Do we need RCTs of double doses?

Screening: There are no RCTs of screening HCWs, patients and visitors that demonstrate prevention of influenza transmission. Screening will be a major undertaking. In a review of testing individuals with Influenza-Like Illness (ILI), Influenza A was detected in less than <25% in many studies (and often <5–7%) and Influenza B <5%, and when comprehensively tested up to 20 respiratory viruses and some bacteria may be detected [54]. Asymptomatic individuals need screening as an average 16% will test positive for Influenza during epidemics.

Furloughing HCWs: There is only one RCT which costed furloughing HCWs but did not assess the effect on influenza transmission to patients.

Influenza supershedders: There are no RCTs of the effects of identifying and isolating supershedders on transmission. They shed dramatically more influenza with larger cough volumes than the average [7–11].

Mask-wearing and hand-hygiene: RCTs of directly- and electronically continuously-observed mask-wearing and hand-hygiene and effects on transmission are needed.

Hospital cleaning: Influenza on fomites lasts longest on stainless steel and non-porous surfaces such as latex gloves and shorter times on soft surfaces and hands (unless replenished) [31–35]. A wide range of chemicals are effective to clean hospital rooms and equipment against influenza [47–49]. The three systems that clean rooms with hydrogen peroxide vapor are effective against influenza and a wide range of bacterial pathogens and clean areas cleaners do not clean. Research into shortening the cleaning cycle is required to increase the likelihood of its widespread adoption.

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