Vaccine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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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ARTICLE INFO

Article history:
Received 26 July 2015
Received in revised form 25 April 2016
Accepted 29 April 2016
Available online xxx

Keywords:
Seasonal influenza
Screening
Transmission
Vaccination
Masks
Respirators
Hand-washing
Hospital cleaning

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.

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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http://dx.doi.org/10.1016/j.vaccine.2016.04.096
0264-410X/

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

Please cite this article in press as: Thomas RE. Do we have enough evidence how seasonal influenza is transmitted and can be prevented in hospitals to implement a comprehensive policy? Vaccine (2016), http://dx.doi.org/10.1016/j.vaccine.2016.04.096