

Transmission of Influenza: Implications for Control in Health Care Settings

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Annual influenza epidemics in the United States result in an average of >36,000 deaths and 114,000 hospitalizations. Influenza can spread rapidly to patients and health care personnel in health care settings after influenza is introduced by visitors, staff, or patients. Influenza outbreaks in health care facilities can have potentially devastating consequences, particularly for immunocompromised persons. Although vaccination of health care personnel and patients is the primary means to prevent and control outbreaks of influenza in health care settings, antiviral influenza medications and isolation precautions are important adjuncts. Although droplet transmission is thought to be the primary mode of influenza transmission, limited evidence is available to support the relative clinical importance of contact, droplet, and droplet nuclei (airborne) transmission of influenza. In this article, the results of studies on the modes of influenza transmission and their relevant isolation precautions are reviewed.

IMPACT OF HEALTH CARE FACILITY-ACQUIRED INFLUENZA

Epidemics of influenza in the United States result in an annual average of >36,000 deaths [1] and 114,000 hospitalizations [2]. Outbreaks of influenza among patients have been described in both long-term care and acute care facilities. During outbreaks in nursing homes, attack rates of >60% have been reported. Among those with influenza, 52% can develop pneumonia, 29% can be hospitalized, and 10% can die of influenza-related complications [3–6]. Influenza illness in other vulnerable patient populations, particularly immunocompromised populations, such as bone marrow transplant recipients or intensive care unit patients, can also result in devastating consequences, with severe, prolonged, and often fatal disease [7–12]. Even among patients on general adult and pediatric wards, health care facility-acquired influenza can result in an increased length of hospital stay and added costs for testing and treatment [13, 14].

The overall burden of health care facility-acquired influenza is uncertain. However, influenza outbreaks occur frequently in

nursing homes and may occur more than once in a single facility during an influenza season [6, 15–17]. Influenza outbreaks in acute care settings are identified and reported less frequently than in long-term care settings, perhaps because there is generally more rapid patient turnover among acute care populations. During the influenza season, however, active surveillance in hospitals has effectively identified health care facility-acquired outbreaks [17–24]. Information from settings with even more rapid patient turnover (e.g., urgent care settings) is lacking. In this article, we review the evidence for mechanisms of influenza transmission and discuss the relevance of these data to the practical application of prevention measures in the health care setting.

TRANSMISSION IN THE HEALTH CARE SETTING

The originating source of health care facility-acquired influenza is often unknown and unrecognized. Visitors and health care personnel with asymptomatic or mild influenza illness acquired from community or patient contacts can spread virus to susceptible patients and staff. Influenza can then spread rapidly among patients and staff, particularly in closed settings [7, 13, 16, 19–23]. Health care personnel often continue to work despite being ill [25–27], increasing the exposure of coworkers and patients to influenza.

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PATHOGENESIS OF INFLUENZA

Influenza viruses infect the columnar epithelium lining the respiratory tract and can cause infection in both the upper and lower airways. The typical incubation period is 2 days, with a range of 1–4 days [28]. Although primary infection in young children is usually symptomatic, overall, ~50% of influenza infections may be asymptomatic. Nevertheless, infected persons with few or no signs of illness may shed virus and, therefore, be infectious to others [29]. Infected persons can become contagious (i.e., they can shed detectable amounts of influenza virus) the day before symptoms begin. Adults usually shed virus for ~3–5 days [28, 30] whereas young children can shed virus for up to 3 weeks [31–33]. Severely immunocompromised persons have been reported to shed influenza virus for even longer periods [34, 35].

Studies generally have shown that susceptibility to influenza infection, preexisting antibody titer, viral shedding, and symptomatic illness are related in the following ways:

- The higher a person's existing antibody titer against the same or a related influenza virus strains, the larger the inoculum of virus needed for infection and the less likely that clinical illness will develop [28, 36].
- The amount of viral shedding correlates with the severity of illness and temperature elevation [31].
- The amount of virus required to induce infection is inversely related to the size of infectious particles administered, with particles <10 μm in diameter more likely to cause infection in the lower respiratory tract [36].

In human volunteer studies, intranasal droplet administration was associated with milder disease than was inhalation of smaller (i.e., <10- μm) particles [36] and required a larger inoculum of virus [37]. Sneezing, coughing, and even talking can produce droplets of a wide variety of particle sizes, which can facilitate either droplet or droplet nuclei spread [38].

MEASURES TO PREVENT TRANSMISSION OF INFLUENZA IN HEALTH CARE FACILITIES

Vaccination. In health care settings, influenza is best prevented by vaccination of both patients and health care personnel. Vaccination of health care personnel has been associated with a decrease in the prevalence of influenza illness among patients and mortality in long-term care facilities [39, 40], where outbreaks of influenza are frequent. Despite the known benefits, vaccination rates among health care personnel in the United States are low, at ~38% [2].

Vaccination of nursing home residents has been associated with reductions in the risk of outbreaks, hospitalization, and death [3, 6]. In the United States, vaccination of nursing home residents is generally high, with reported rates of 64%–83%

[2]. However, most influenza-related hospitalizations occur among noninstitutionalized persons, particularly persons aged ≥ 65 years and persons aged <65 years with underlying medical conditions [41, 42]. Among persons aged ≥ 65 years, 64% were vaccinated in 2000 [2]. The proportion of persons aged <65 years who had high-risk conditions and who received influenza vaccine was even lower, at 32% [2]. Although vaccination of hospitalized patients at risk for influenza-related complications has been recommended for many years, it often is not accomplished, representing a missed opportunity for prevention [43]. Efforts to increase compliance with vaccination of high-risk persons, either as outpatients or during hospitalizations, could substantially reduce the impact and costs of influenza on the health care system.

In addition to vaccination, other prevention measures are necessary to reduce influenza transmission in health care settings, because some high-risk persons, especially immunocompromised patients, can mount an inadequate immunologic response to vaccination. In addition, the vaccine and predominant circulating virus strains may not be well matched antigenically (this happens ~1 of every 10 years; Centers for Disease Control and Prevention, unpublished data), reducing the effectiveness of vaccination.

Antiviral medications. Antiviral medications for influenza can be a helpful adjunct to vaccination and are available both for treatment and prophylaxis of influenza [2]. These medications can effectively reduce the spread of influenza in a health care facility when used in conjunction with other control measures, including isolation precautions and vaccination [5, 8, 15, 17, 24, 25, 33]. Guidelines for the use of antiviral medications during influenza outbreaks in health care facilities have been published [2, 44–45].

Isolation precautions. A variety of infection-control measures are used for decreasing the risk of transmission of infectious agents in health care facilities. Transmission-based precautions are based on the predominant route(s) of infection and may be combined for diseases that have multiple routes of transmission. Isolation precautions can be an important part of efforts to prevent transmission of respiratory viruses, if compliance can be maintained and if the infection-control procedures used are effective barriers to the mode of spread of the virus.

The 3 modes of transmission relevant to influenza that are described in the recommendations for isolation precautions in hospitals published by the Healthcare Infection Control Practices Advisory Committee include contact transmission, droplet transmission, and airborne transmission [46].

Contact transmission is further divided into direct and indirect contact transmission. Direct transmission involves body-to-body surface contact, and indirect transmission occurs via

contact with contaminated intermediate objects, such as contaminated hands, or inanimate objects, such as needles or countertops.

Droplet transmission occurs when contagious droplets produced by the infected host through coughing or sneezing are propelled a short distance and come into contact with another person's conjunctiva, mouth, or nasal mucosa. Because these droplets generally are large ($>10\ \mu\text{m}$) and do not stay suspended in the air, this mode of transmission is not affected by special air handling or control of room pressures.

Airborne transmission entails the production of infectious droplet nuclei, generally $<5\ \mu\text{m}$ in diameter, which, in contrast to droplets, can remain suspended in the air and be disseminated by air currents in a room or through a facility to be inhaled by a susceptible host. Preventing the spread of droplet nuclei requires the use of special air-handling and ventilation procedures.

The influenza isolation precautions in the "1994 Guidelines for Prevention of Nosocomial Pneumonia" [45] for patients with suspected or confirmed influenza are aimed at preventing transmission by contact, droplet, and airborne routes. These recommendations are as follows:

- The patient should be placed in a private room or a room with another influenza-infected patient.
- As much as feasible, the patient should be placed in a negative air-pressure room or placed together with other patients with suspected or proven influenza in an area of the hospital with an independent air supply and exhaust system.
- Health care personnel should wear a mask when entering the room of a patient with known or suspected influenza.
- Health care personnel should use standard plus droplet and contact precautions, including hand washing, and use of gloves, gown, and eye protection, if they are likely to come into contact with body fluids or contaminated surfaces [45].

Prioritizing the importance of any or all of these recommended procedures for influenza prevention is hindered by the lack of data demonstrating their relative efficacy in various health care settings. Droplet transmission is most often reported to be the primary means of person-to-person transmission of influenza, suggesting that the use of many of the less costly precautions, such as cohorting influenza-infected patients and the use of masks and hand hygiene, could offer appreciable benefit. However, other measures designed to interrupt airborne transmission, such as the use of negative air-pressure rooms, can be problematic and expensive.

EVIDENCE FOR CONTACT TRANSMISSION

Studies reported by Bean et al. [47] indicated that spread of infection by contact with contaminated fomites is possible.

They showed that human influenza viruses could survive on a variety of surfaces at 35%–49% humidity and a temperature of 28°C. Both influenza A and B viruses were cultured from experimentally contaminated, nonporous surfaces, such as steel and plastic, up to 24–48 h after inoculation, and from cloth, paper, and tissues up to 8–12 h after inoculation. However, viruses could be recovered from hands for only 5 min and only if the hands were contaminated with a high viral titer. Viable virus could be transferred from nonporous surfaces to hands for 24 h and from tissues to hands for 15 min. These data support the feasibility of spread of influenza by indirect contact. However, the importance of this mode of transmission probably depends on the type of surface and the amount of virus present.

A clinical study on hand washing has shown a reduction in the total rate of respiratory illnesses [48]. In addition, one study also demonstrated the effect of hand sanitation on influenza using 95% ethanol, which demonstrated viricidal activity against influenza viruses on the hands [49]. Although the effectiveness of hand washing and the use of other forms of hand hygiene on influenza transmission has not been studied, this measure is prudent, given the environmental survival of influenza viruses [50].

STUDIES OF TRANSMISSION IN MICE

Animal studies have been conducted to elucidate factors affecting influenza transmission. Loosli et al. [51] evaluated the effects of humidity on the ability of influenza viruses to infect mice in a nonventilated room with constantly agitated air. At a relative humidity of 17%–24%, animals became infected with influenza as late as 24 h after the virus was first aerosolized into the room, although the proportion of animals infected decreased over time (figure 1). Infectivity was enhanced at 22 h after influenza virus was introduced, when the floor was vigorously swept, suggesting that desiccation of the virus does not eliminate infectivity. Whether sufficient numbers of virus-laden particles can remain viable to infect humans in a similar setting is unknown.

Mouse experiments by Schulman [52, 53] found a strong inverse correlation between infection rate and air exchange, regardless of whether infected and uninfected mice were physically separated. Uninfected mice also were as likely to become infected when housed in the same cage with infected mice as they were if housed in an adjacent, separate cage that allowed droplet and droplet nuclei transmission between cages but no direct contact. This suggests that droplet transmission occurred between cages. Infectious particles of $<10\ \mu\text{m}$ in diameter produced by infected mice were found by air sampling, further suggesting that airborne transmission of droplet nuclei could have occurred. Whether these findings may be extrapolated to

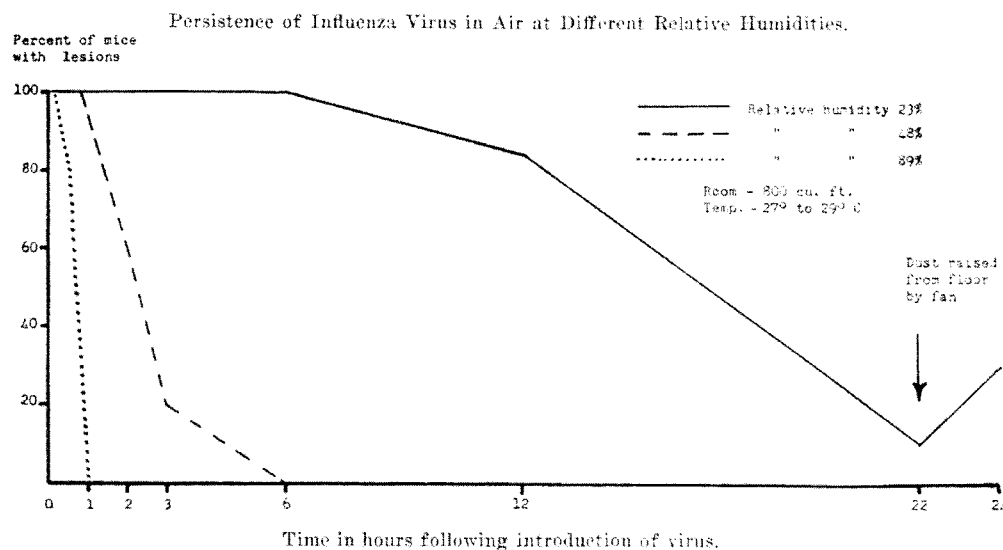


Figure 1. Percentage of mice placed in a room at different relative humidity levels and different time periods following atomization of influenza viruses that caused pulmonary infections. Reproduced from [51].

humans, particularly those with preexisting antibody levels to influenza, is unclear.

STUDIES INVOLVING HUMANS

Our review found no human experimental studies published in the English-language literature delineating person-to-person transmission of influenza. This stands in contrast to several

elegant human studies of rhinovirus and respiratory syncytial virus transmission, which were recently summarized by Goldmann [54]. Thus, most information on human-to-human transmission of influenza comes from studies of human inoculation with influenza virus and observational studies.

Early studies on influenza in humans found that illness could be induced with substantially lower virus titers when influenza virus was administered as a small droplet aerosol rather than

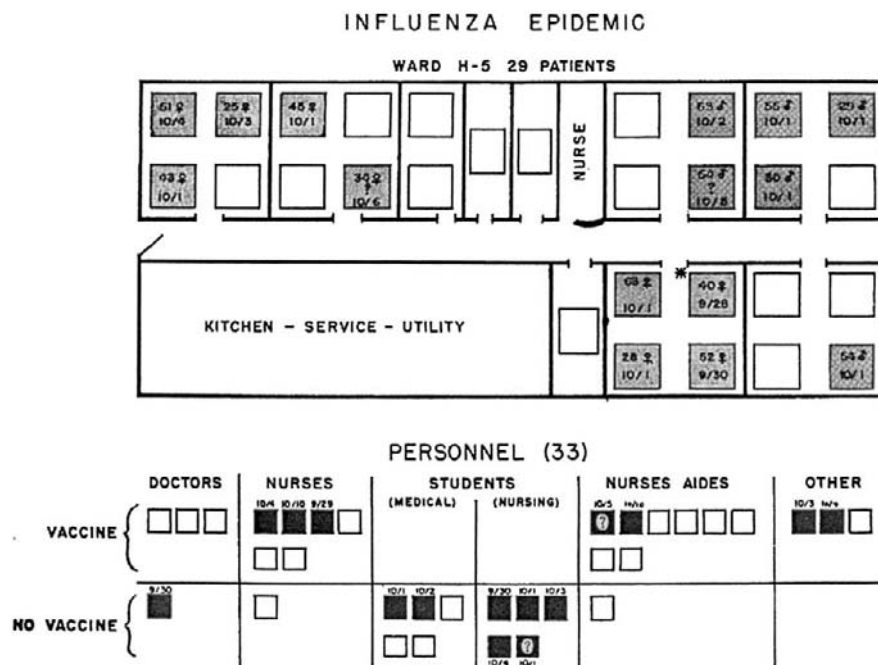


Figure 2. Diagram of the hospital ward and dates of illness onset among patients. *Index case. Reproduced from [21].

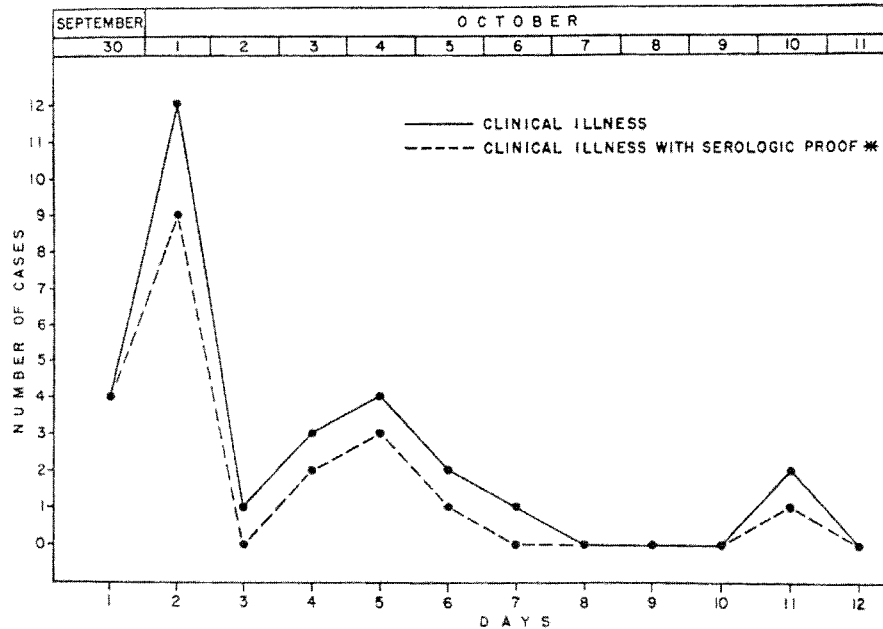


Figure 3. Epidemic curve of the number and onset of influenza-like illnesses among patients and health care personnel on a medical ward after introduction of influenza by a single case patient on day 0. Reproduced from [21].

as nasal droplets, suggesting that infection is induced most efficiently when virus is deposited in the lower respiratory tract rather than the upper respiratory tract [37]. Although these data support the probability of droplet nuclei transmission of influenza, the proportion of nonexperimental influenza infections acquired through droplet nuclei, compared with droplet spread, is not known.

Early in the 1958–1959 pandemic, the hospitalization of a single infected patient before the onset of influenza activity in the community provided an opportunity to study the spread

of influenza within a hospital ward [21]. The febrile, acutely ill patient was admitted (with no isolation precautions) to a 4-person room. Two days later, 3 health care personnel and the patient housed nearest to the index case patient became ill. The following day, the patient's other 2 roommates, additional health care personnel, and 7 patients scattered throughout the rest of the hospital ward became ill (figure 2). The pattern of the spread of influenza throughout this ward suggests that health care personnel helped disseminate infection through either contact or droplet spread. However, the authors do not

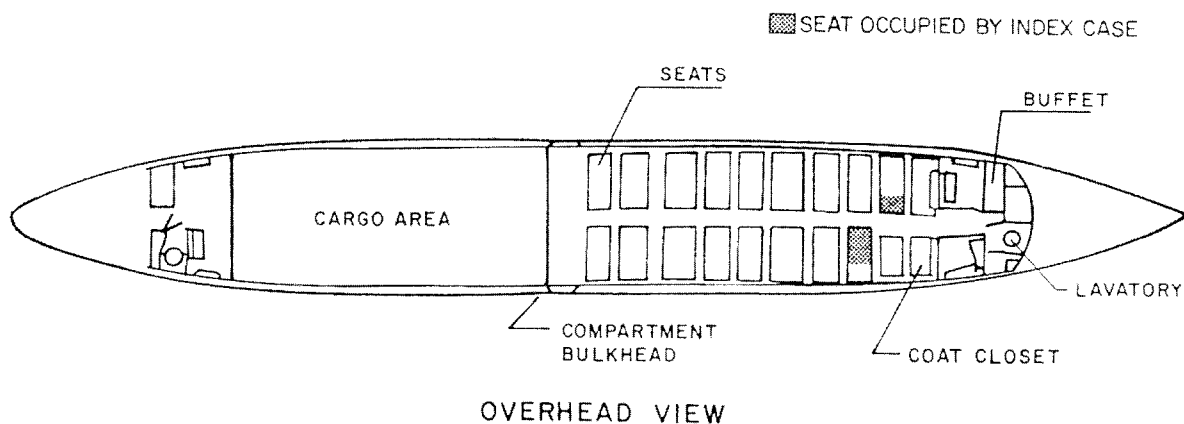


Figure 4. Diagram of the airplane and location of the index patient in relation to the aircraft facilities. Reproduced from [55].

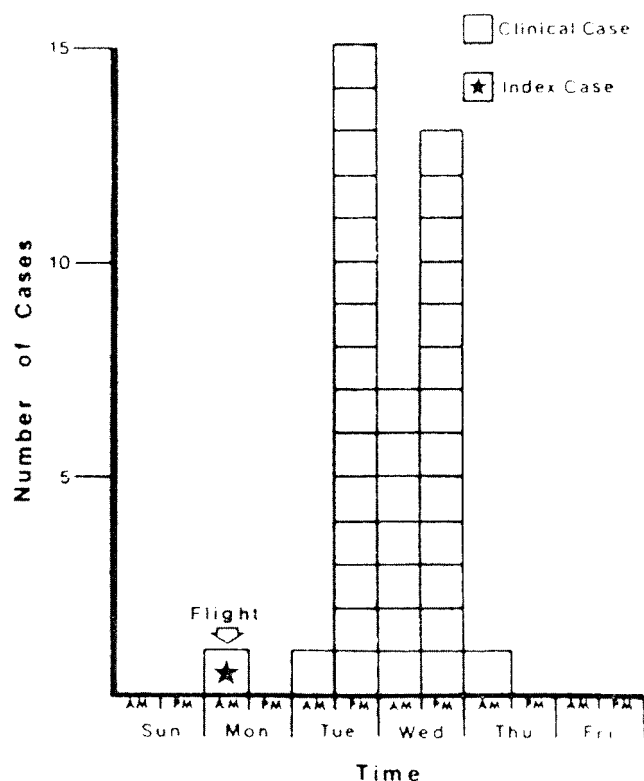


Figure 5. Epidemic curve of influenza-like illness among airplane passengers and crew exposed to an acutely ill passenger infected with influenza A (H3N2). Reproduced from [55].

provide information regarding which specific health care personnel cared for specific patients. The epidemic curve suggests an initial point-source outbreak with subsequent person-to-person spread, and not a single source outbreak in which all identified cases occurred within a short time frame, as would be anticipated if airborne transmission were the principal mode of spread (figure 3).

In contrast, an observational study by Moser et al. [55] is more suggestive of airborne transmission of influenza among the passengers and the crew of a single aircraft. An airplane with 5 crew members and 49 passengers was detained in Homer, Alaska, for 4.5 h, including 2–3 h when the ventilation system was turned off. A passenger, acutely ill with fever and cough and subsequently found to be infected with a new (drifted) influenza A (H3N2) strain, stayed on the plane, near the coat closet, buffet, and lavatory, the entire 4.2-h period, along with 30 other passengers. The remaining passengers and crew members periodically left and reboarded the plane (figure 4). Seventy-two percent of the crew and passengers developed influenza-like illness, and 91% of those tested were found to have laboratory-confirmed influenza. The epidemic curve was consistent with a point-source outbreak (figure 5). Some passengers, including the index case patient, subsequently flew on another plane to Kodiak, Alaska, whereas the crew and re-

maining passengers flew first on a separate flight. No difference existed in the attack rates between these 2 groups, suggesting that additional exposure in an airplane with standard ventilation did not increase the risk of illness. Although airborne transmission is a possible explanation for the primary spread of influenza during this outbreak, droplet transmission cannot be excluded, because most (if not all) of the crew members and passengers would have passed within <1 m of the coughing index patient on their way to the various aircraft facilities. However, the high illness rate in the setting of a nonfunctioning ventilation system suggests a role for airborne transmission.

An observational study among patients with tuberculosis during the 1957–1958 influenza pandemic more strongly supports a primary role for airborne spread of influenza [56]. Patients in one building were housed in rooms with UV lights on the ceiling, whereas patients in other buildings did not have UV lights in their rooms. During an outbreak of influenza, the illness rate was 19% among those in rooms without UV lights and only 2% among those in rooms with ultraviolet lights. Although UV radiation is apt to help control airborne transmission, the lack of an outbreak among patients in the building without UV lights could have resulted from the chance that the virus was not introduced into the building. If radiated and nonradiated rooms had been located in close proximity in the same building, the evidence of airborne transmission would have been much stronger.

Saldado et al. [18] recently summarized observations of in-hospital transmission of influenza at the University of Virginia (Charlottesville) and noted the rare occurrence of health care facility-acquired influenza despite the predominant use of private positive pressure rooms. Experience at the University of Rochester Medical Center (Rochester, NY) was similar in that most cases of influenza acquired during hospitalization among pediatric patients were observed among patients housed in the same room, particularly those in the cribs adjacent to the index case patient. Patients in adjacent rooms or across hallways were less likely to become infected, even though doors remained open and rooms designed to prevent airborne transmission were not used (C.B.H, unpublished data). These observations point to either large droplet or contact transmission as the predominant modes of transmission on hospital wards.

CONCLUSIONS

Evidence exists to support the transmission of influenza viruses by direct and indirect contact and by droplet and droplet nuclei (i.e., airborne) transmission. However, experimental studies involving humans are limited [37, 47], and the relative contribution of each mode of transmission remains unclear. Furthermore, the relative importance of airborne transmission in a setting of normal air exchange is unknown. The use of current

droplet and contact precautions assumes placement of patients in rooms with standard air exchange rates [45] and not the stagnant air conditions reported in the study by Moser et al. [55]. Whether the use of negative-pressure rooms would result in a measurable decrease in the rate of transmission, compared with the use of droplet precautions in a private positive-pressure room with appropriate air exchange and ventilation, is unknown and may only be determined through carefully planned studies.

In addition to determining the clinical importance of airborne transmission, practical considerations also need to be taken into account. The limited number of beds in negative-pressure rooms may be quickly filled during community-wide influenza outbreaks, making implementation of airborne transmission precautions impractical. Determining the necessity of isolation of influenza-infected patients in negative-pressure rooms is important for planning by health care facilities for epidemic periods when health care systems may be inundated with influenza-related admissions. Nevertheless, given the uncertainty of the clinical importance of airborne transmission of influenza, use of negative-pressure rooms for patients with confirmed or suspected influenza may be prudent if they are housed near severely immunocompromised persons. These precautions may also be advisable for initial admissions of persons infected with a newly emergent influenza A subtype with pandemic potential. Immunity in the general population to such a virus would be poor, and the viral inoculum necessary for infection may be low. An example would be the use of negative-pressure rooms for persons admitted to Hong Kong hospitals in 1997 with influenza A (H5N1) infections [57].

Regardless of the isolation precautions used to prevent influenza acquired in health care settings, the primary preventive measure for influenza remains vaccination. Improved rates of vaccination of all persons at increased risk of influenza-related complications, their household contacts, and health care personnel, would substantially limit the introduction of influenza into health care facilities and impede person-to-person transmission when influenza is introduced.

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