

Transmission of influenza A in human beings



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Planning for the next influenza pandemic is occurring at many levels throughout the world, spurred on by the recent spread of H5N1 avian influenza in Asia, Europe, and Africa. Central to these planning efforts in the health-care sector are strategies to minimise the transmission of influenza to health-care workers and patients. The infection control precautions necessary to prevent airborne, droplet, and contact transmission are quite different and will need to be decided on and planned before a pandemic occurs. Despite vast clinical experience in human beings, there continues to be much debate about how influenza is transmitted. We have done a systematic review of the English language experimental and epidemiological literature on this subject to better inform infection control planning efforts. We have found that the existing data are limited with respect to the identification of specific modes of transmission in the natural setting. However, we are able to conclude that transmission occurs at close range rather than over long distances, suggesting that airborne transmission, as traditionally defined, is unlikely to be of significance in most clinical settings. Further research is required to better define conditions under which the influenza virus may transmit via the airborne route.

Introduction

The current avian influenza epidemic, which is affecting birds in Eurasia and Africa, has heightened world awareness about the possibility of a human influenza pandemic resulting from either antigenic drift or avian viral reassortment with a human strain.¹ Pandemic planning has been accelerated and is occurring at many levels, from primary care to national governments worldwide.²⁻⁴

Despite 70 years of research since the influenza virus A was discovered,⁵ there continues to be vocal debate about the modes of influenza transmission, specifically whether influenza is transmitted via the airborne route, via the droplet or contact route, or a combination of these routes. Establishing how influenza is transmitted under different circumstances, and whether transmission requires close contact, is of great importance because the results will have a major influence on the choice of infection control measures in health-care settings.

Airborne precautions involve special ventilation controls, and to a lesser extent specialised masks (respirators), to prevent transmission. According to standard definitions, close contact is not required for airborne transmission to occur.^{6,7} Necessitating the use of airborne precautions during a pandemic would require extraordinary resources and substantial advance planning; acknowledgment of a significant contribution of airborne transmission will affect where patients should be treated, how they would be triaged, the use of antiviral agents, and the choice of personal protective equipment. However, preventing droplet and contact transmission would require quite different control measures, since close contact with an infected case would typically be required for transmission to occur.

Some resolution to this debate is urgently needed. To better inform current infection control guidelines and continuing pandemic planning efforts, we did a systematic review of the English language literature in an attempt to assess the evidence about the routes of influenza transmission. Previous investigators have

identified categories of evidence that should be considered when attempting to determine the modes of transmission of a respiratory pathogen, including: survival of the pathogen in the environment; experimental infections in laboratory animals and in human beings; and epidemiological studies of naturally occurring and laboratory-acquired infections.⁸ We have applied this framework specifically to influenza transmission in this review.

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Panel: Possible modes of respiratory virus transmission^{6,7}

Direct contact

Transmission occurs when the transfer of microorganisms results from direct physical contact between an infected or colonised individual and a susceptible host.

Indirect contact

Transmission occurs by the passive transfer of microorganisms to a susceptible host via an intermediate object such as contaminated hands that are not washed between patients, or contaminated instruments or other inanimate objects in the patient's immediate environment.

Droplet

Transmission occurs via large droplets ($\geq 5 \mu\text{m}$ diameter) generated from the respiratory tract of the infected individual during coughing or sneezing, talking, or during procedures such as suctioning or bronchoscopy. These droplets are propelled a distance of less than 1 m through the air and are deposited on the nasal or oral mucosa of the new host or in their immediate environment. These large droplets do not remain suspended in the air; therefore, special ventilation is not required since true aerosolisation does not occur.

Airborne

Transmission occurs via the dissemination of microorganisms by aerosolisation. Organisms are contained in droplet nuclei (airborne particles less than $5 \mu\text{m}$ that result from the evaporation of large droplets) or in dust particles containing skin squamous cells and other debris that remain suspended in the air for long periods of time. Such microorganisms are widely dispersed by air currents and inhaled by susceptible hosts who may be some distance away from the source patients or individuals, even in different rooms or hospital wards. Control of airborne transmission is the most difficult because it requires control of airflow through special ventilation systems.

Contact transmission includes direct contact, indirect contact, and droplet (large droplet) transmission.

Methods

Articles of interest included only those that provided evidence for the route of influenza virus transmission in mammals. We specifically concentrated on whether a study provided evidence that a particular mode of transmission of the virus could be definitively ruled out of or into the exclusion of other modes of transmission. The standard US Centers for Disease Control and Prevention and Public Health Agency of Canada definitions used for the modes of transmission are shown in the panel.^{6,7}

Experimental studies, as well as retrospective or prospective observational studies, were considered for inclusion. Reports of outbreaks were included if they provided detailed, specific information on any of the following topics: the type of control measures used; mapping of the pattern of transmission within a confined area; or a discussion of the potential route of transmission. Review articles were excluded, as were articles in languages other than English.

The following databases were searched to the earliest possible date for relevant articles: Medline, EBM Reviews, Embase, CINAHL, and Healthstar. Search terms used were as follows: “transmission”, “spread”, “dissemination”, “droplet”, “airborne”, “contact”, “fomite”, “aerosol”, “outbreak”, “epidemic”, and “influenza”. With the same databases, the following search terms were used to identify articles relevant to the behaviour of influenza in the environment: “influenza”, “survival”, “decay”, “viability”, “stability”, “virus”, “environment”, “surface”, “fomite”, “airborne”, and “aerosol”.

Two reviewers did the searches independently. The initial search resulted in 2012 citations (figure). Article titles and abstracts were reviewed for relevance by at least two reviewers and rejected if they did not relate to the route of transmission of influenza. At least two reviewers needed to agree that a study met the inclusion criteria for it to move to the second round of review.

Articles accepted at the abstract stage (136 papers) were each reviewed in their entirety by at least two researchers,

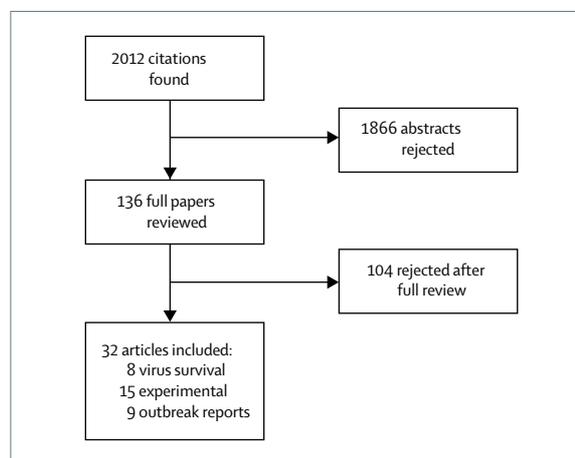


Figure: Flow diagram of the process and results of article selection

	Exposed cells or animal	Duration of virus survival	Virus detected 1 min after spray
Hemmes et al ¹⁰			
30–40%	Chick embryos	>90 min	..
60–70%	Chick embryos	30 min	..
Loosli et al ¹¹			
>80%	Mice	1 h	..
<55%	Mice	>6–24 h	..
Wells and Brown ¹²			
	Ferrets	1 h	..
Schaffer et al ¹³			
50%	Erythrocytes	..	3–30%
70%	Erythrocytes	..	6–34%

All samples used were air samples. ..=not done.

Table 1: Studies of influenza virus survival in artificial aerosols, by relative humidity

	Duration of survival (h)	
	Mitchell et al ¹⁴	Mitchell and Guerin ¹⁵
Human	6–15	9–16
Avian	24–36	24–36
Swine	..	16
Equine	..	21–30

..=not applicable.

Table 2: Survival of different viral strains of artificially aerosolised influenza in air samples on chick embryos

after which a panel of four researchers discussed their inclusion. Reference lists of relevant articles were searched for additional articles. In total, 32 articles were considered relevant to this review. Three reviewers abstracted the data using a standardised form designed by the investigators, which included a tool to assess study quality.⁹

Results

Survival of the influenza virus in the environment

Six experimental studies examining the survival of influenza as an aerosol were reviewed.^{10–15} These studies showed that, in general, different strains of influenza virus remain viable if artificially aerosolised from a liquid suspension, and retain their infectivity to several different host cell types (table 1 and table 2). Specifically, erythrocytes, chick embryos, mice, and ferrets were all shown to be capable of acquiring infection via this route. Influenza was detected in air samples for up to 24 h after aerosolisation at low levels of relative humidity and for up to 60 min at higher levels of relative humidity (table 1).^{10,11} Similarly, ferrets inoculated with material collected from air containing aerosolised influenza became infected if the exposure occurred within 1 h of aerosolisation.¹² Conversely, by use of several different preparations of aerosolised influenza, Schaffer and colleagues¹³ reported that only 3–30% and 6–34% of influenza virus could be detected in the air 1 min after aerosolisation at moderate and high

levels of relative humidity, respectively. Two studies showed that the rate of decay of aerosolised influenza is higher in human and swine strains than in avian strains (table 2), illustrating the important point that different strains might have different survival characteristics.^{14,15}

Two studies provided evidence that strains of influenza virus are able to survive on surfaces.^{16,17} Transmission of the virus has been documented to occur from porous and non-porous surfaces to the hands of volunteers in large enough quantities to potentially cause disease.¹⁶ Non-porous surfaces were capable of supporting viable virus transfer for a substantially longer period (up to 2 h) than porous surfaces. This study did not attempt to document actual infection resulting from surface acquisition.¹⁶ Boone and Gerba¹⁷ recovered viable influenza virus from various objects in homes and day-care centres where children ill with influenza-like symptoms were present.¹⁷ Influenza virus was detected on 23% and 53% of inanimate objects present in the day-care centres in the autumn and spring, respectively, and approximately 60% of objects swabbed in the homes of sick children were contaminated with the virus. Again, infection resulting from contact with contaminated objects in the environment was not investigated.

Experimental infections in laboratory animals and human beings

15 studies that examined experimental infection in animals and human beings were reviewed (table 3 and table 4). Six studies investigated animal-to-animal transmission,^{18–23} whereas nine compared different methods of artificial inoculation.^{24–32} 13 of the 15 studies showed that clinical influenza could be produced in mice, ferrets, ponies, squirrel monkeys, and human beings exposed to an aerosolised suspension of the influenza A virus.^{18,20–29,31,32} Four of the six animal-to-animal studies showed transmission of influenza between aerosol-infected animals and healthy animals housed together (table 3).^{18,21–23} One study showed that virus could be detected in the air surrounding infected mice during the period of infectiousness.²³

Recognition of the limitations of studies that did not control for different modes of transmission led to further experiments being designed to isolate the airborne route as the sole explanation for transmission. In an often-cited study from the 1960s, Schulman and Kilbourne²⁰ showed that influenza could be transmitted between mice physically isolated by a double mesh-wire screen to maintain a 2 cm separation. The rate of infection in exposed mice was no different in this setting than when the exposed mice were housed in the same cage with the source mice.²⁰

With a more complicated environmental design, Andrewes and Glover¹⁸ studied the transmission of an influenza A strain between ferrets. They showed that transmission occurred between source and exposed animals despite being housed in separate open-wire-

	Animal	Method of influenza virus exposure	Diagnostic criteria used to confirm infection
Andrewes and Glover ¹⁸	Ferrets	Exposure to animals infected via aerosol	Clinical or pathology; serology
Nakanishi ¹⁹	Mice	Exposure to intranasally inoculated animals	Clinical or pathology; serology
Schulman and Kilbourne ²⁰	Mice	Exposure to mice infected via aerosol separated by wire mesh	Clinical or pathology
Schulman and Kilbourne ²¹	Mice	Exposure to animals infected via aerosol	Viral isolation
Schulman and Kilbourne ²²	Mice	Exposure to animals infected via aerosol	Viral isolation
Schulman ²³	Mice	Exposure to animals infected via aerosol	Viral isolation

Table 3: Experimental studies of animal-to-animal transmission of influenza

	Population	Method of influenza virus exposure	Diagnostic criteria used to confirm infection
Smorodintseff et al ²⁴	Human	Aerosol	Clinical or pathology; serology
Wells and Henle ²⁵	Mice	Aerosol	Clinical or pathology
Loosli et al ²⁶	Mice	Intranasal vs aerosol	Clinical or pathology
Alford et al ²⁷	Human	Aerosol	Clinical or pathology; viral isolation; serology
Knight ²⁸	Human	Intranasal vs aerosol	Serology
Frankova ²⁹	Mice	Intranasal vs aerosol	Clinical or pathology; antigen detection
Little et al ³⁰	Human	Natural vs intranasal	Serology
Snyder et al ³¹	Squirrel monkey	Intranasal vs aerosol	Serology
Mumford et al ³²	Pony	Intranasal vs aerosol	Clinical or pathology; viral isolation; antigen detection; serology

Table 4: Experimental studies of different methods of influenza inoculation in animals and human beings

meshed cages with the exposed animals placed 1 m higher and 1.6 m away from the source animals. They further showed that transmission occurred between source and exposed animals when they were separated by approximately 2.5 m long S-shaped and U-shaped closed ducts, with the direction of airflow from source towards exposed animals.¹⁸

Five studies have compared experimental intranasal inoculation with inhalation of aerosolised virus (table 4). Snyder and co-workers³¹ reported similar rates of laboratory-confirmed infection after exposure to aerosolised virus compared with intranasal administration in squirrel monkeys. Frankova²⁹ reported both methods to be effective in producing laboratory-confirmed infection in mice, but found that the timing of viral replication differed: replication occurred simultaneously in all parts of the respiratory tract when the virus was administered in aerosol form, whereas intranasal administration resulted in viral replication occurring in the lung before the trachea and the nasal mucosa by 4–8 h and 21–24 h, respectively.²⁹ By contrast, Mumford and colleagues³² reported that exposure to aerosolised virus resulted in more severe clinical symptoms than intranasal inoculation in ponies. Loosli and co-workers²⁶ suggested that a smaller quantity of virus was required to produce clinical infection and death in mice through intranasal inoculation than with

	Number	Setting	Population	Case identification	
				Diagnostic criteria	Number (%) laboratory tested
Blumenfeld et al ³³	62	Hospital	Medical patients and staff	Viral isolation; serology	55 (89%)
McLean ³⁴	1116	Hospital housing tuberculosis patients	Medical patients and staff	Clinical; serology	1116 (100%)
Moser et al ³⁵	53	Aircraft	Healthy adults	Clinical; viral isolation; serology	Unclear
Klontz et al ³⁶	110	Naval base aircraft	Healthy adults	Clinical; viral isolation; serology	105 (95%)
Morens and Rash ³⁷	39	LTCF	Elderly residents	Clinical; viral isolation; serology	37 (95%)
Drinka et al ³⁸	690	LTCF	Elderly residents	Viral isolation	241 (35%)
Munoz et al ³⁹	15	NICU	Critical care neonates	Clinical; viral isolation; antigen detection	4 (27%)
Cunney et al ⁴⁰	54	NICU	Critical care neonates	Clinical; antigen detection	54 (100%)
Awofeso et al ⁴¹	59	Correctional facility	Healthy adults	Clinical; viral isolation; antigen detection	21 (36%)

LTCF=Long-term care facility; NICU=neonatal intensive care unit.

Table 5: Summary of influenza epidemiological studies

aerosol inhalation. However, the investigators admitted that they could not easily quantify the amount of virus inhaled.²⁶

Few experimental studies have examined influenza virus transmission in human beings (table 4). Two studies have shown that laboratory-confirmed and clinical influenza infection can be produced in 17–19% of human participants via inhalation of aerosolised virus via a facemask.^{24,27} Neither study assessed person-to-person transmission after the initial exposure. A third study has shown that the dose of artificially aerosolised influenza required to cause human disease is lower than that required for intranasal inoculation.²⁸ A quasi-experimental study compared a cohort of college students with documented influenza A infection acquired naturally during three outbreaks, with healthy volunteers who had been intranasally inoculated with wild type influenza A viruses.³⁰ The experimentally infected group had milder illness and shorter duration of cough. Additionally, those with naturally acquired illness showed more abnormalities in small airway function and increased airway reactivity than those with experimentally induced illness. The investigators suggest that this provides evidence that the pathogenesis of natural influenza A infection involves the deposition of aerosolised virus particles distal to the nasal passages.³⁰

Observational outbreak studies of natural influenza in human beings

A summary of the nine observational studies included in this review is shown in table 5. The outbreak populations included patients and staff on a medical ward,^{33,34} critical care neonates,^{39,40} elderly residents of long-term care facilities,^{37,38} and healthy adults.^{35,36,41} Influenza cases were identified by clinical symptoms in seven of nine studies, and by at least one laboratory method in all nine. Infection in exposed individuals ranged from 33% to 55% in the unvaccinated and from 0% to 37% in vaccinated cohorts (table 6). All nine studies were observational outbreak

studies with no planned control groups. All studies had the potential for observation bias, and all studies were likely to suffer from one or more of the following: confounding, co-intervention, or chance variation (table 7).

Three of the nine studies have been frequently cited as providing evidence for airborne transmission of influenza.^{34,35,38} McLean³⁴ reported an observational account of the 1957 influenza pandemic in a California veterans' hospital housing tuberculosis patients. The proportion of individuals infected with influenza over two successive outbreaks was substantially lower in the hospital department in which upper air ultraviolet disinfection had been installed versus another department in which it had not been installed (2% vs 19%).³⁴

Moser and colleagues³⁵ gave a detailed description of an influenza outbreak that occurred on an Alaskan Airlines flight. A passenger became acutely ill with laboratory-confirmed influenza A during a stop-over for which the aircraft ventilation was shut down for 3 h. Of passengers confined to the aircraft during the stop-over, 72% became infected with influenza. Passengers moved freely about the cabin during this period and occurrence of infection increased with increasing time spent on the aircraft. The epidemiological and laboratory investigation strongly suggested that the initially ill passenger was the index case and that the passengers who subsequently became ill were likely to have acquired their infection from this individual.

The final observational study suggesting airborne transmission reported an association between influenza infection and ventilation system design in different buildings of a long-term care facility.³⁸ In the newest building, which had a ventilation system that provided 100% outside air, 1.6% of patients were infected. In two buildings that had systems that provided 70% outside air, 15.8% and 9.3% of patients were infected, whereas an older building that provided 30% outside air had an infected proportion of 13.8%.

Six of the nine observational studies reported results that were more suggestive of droplet or contact transmission.^{33,36,37,39,40,41} Four of these studies showed temporal or spatial outbreak patterns that were suggestive of transmission via close person-to-person contact.^{33,36,37,41} Spatial and temporal trends in a hospital outbreak that included both patients and staff showed that within 48 h of symptom onset in the index patient, a patient in an adjacent bed as well as three staff members became ill. These staff members were implicated in transmitting the infection to the 24 new cases with whom they had had close contact over the subsequent 10 days.³³ Of note, isolation precautions were not instituted and patients in single rooms did not acquire infection. An outbreak investigation in the psychiatric ward of a correctional facility found that all inmates in the ward had private rooms and all new cases had close contact with known cases.⁴¹ Despite working in the same area, prison guards were not infected. However, 13% of health-care workers who cared for the prisoners did develop influenza.

An influenza outbreak on a naval base was also associated with recent aeroplane travel.³⁶ 23 (56%) people became ill within 72 h of being on one of two aircraft with 11 ill squadron mates. Both aircraft (McDonnell Douglas DC-9) had fully functioning ventilation systems designed to completely exchange the volume of air in the passenger cabin with 100% fresh air every 4 min (15 air exchanges per hour). Additionally, the airflow was directional from the ceiling to floor with minimum fore-to-aft/aft-to-fore airflow. Interestingly, new cases were fairly evenly distributed throughout the aircraft and were not necessarily close seatmates of the originally ill squadron mates. No comment was made, however, about passenger movement during the flight.

An influenza outbreak investigation on a medical ward reported that nurses, who were assigned the task of administering medications or tube feeding, routinely had ungloved contact with the patients' oral secretions. Retracing the evolution of the outbreak suggested that such contact resulted in a patient-to-patient transmission pattern;³⁷ a higher proportion of patients who were tube fed or frequently suctioned were infected (38%) than other patients (13%; $p=0.08$). Importantly, no illness was detected in direct-care staff or staff in the nursing station, which was located in the centre of the ward's directional airflow.

Cunney and colleagues⁴⁰ reported the results of an influenza outbreak in a neonatal intensive care unit, and found that twin pregnancy (odds ratio 7.0; $p=0.04$, 95% CI 1.1–46) and the requirement for mechanical ventilation (odds ratio 6.2; $p=0.02$, 95% CI 1.35–28) were both independent risk factors for acquisition of the virus. The association between twin pregnancy and influenza was hypothesised to be the result of the parents handling their twins without washing their hands between contact with each child. The association between mechanical ventilation and influenza may have

	Vaccinated	Unvaccinated	Total	Laboratory confirmed
Blumenfeld et al ³³	7/20 (35%)	23/42 (55%)	30/62 (48%)	21/62 (34%)
McLean ³⁴	171/1116 (15%)	171/1116 (15%)
Moser et al ³⁵	38/53 (72%)	28/53 (53%)
Klontz et al ³⁶	25/67 (37%)	16/43 (37%)	41/110 (37%)	Unclear
Morens and Rash ³⁷	10/36 (28%)	1/3 (33%)	11/39 (28%)	6/39 (15%)
Drinka et al ³⁸	83/690 (12%)	68/690 (10%)
Munoz et al ³⁹	0/0	4/11 (36%)	4/11 (36%)	3/11 (27%)
Cunney et al ⁴⁰	0/0	19/54 (35%)	19/54 (35%)	19/54 (35%)
Awofeso et al ⁴¹	22/59 (37%)	9/59 (15%)

..=not reported.

Table 6: Reported infection from influenza epidemiological studies

	Observation bias	Confounding	Co-intervention	Chance variation
Blumenfeld et al ³³	Yes	No	Yes	No
McLean ³⁴	Yes	Yes	No	No
Moser et al ³⁵	Yes	No	Yes	No
Klontz et al ³⁶	Yes	Yes	No	No
Morens and Rash ³⁷	Yes	No	Yes	No
Drinka et al ³⁸	Yes	Yes	Yes	Yes
Munoz et al ³⁹	Yes	No	No	Yes
Cunney et al ⁴⁰	Yes	No	Yes	Yes
Awofeso et al ⁴¹	Yes	No	No	No

Observation bias occurs when the method of observation used causes the results to be skewed in some non-random manner, leading to inaccurate results. Confounding occurs when an observed association between an exposure and outcome is altered by a third factor. Co-intervention is when treatment is given in addition to the experimental treatment and can alter study results. Chance variation occurs when the results obtained from a study are because of random differences between individuals.⁹

Table 7: Results of the critical appraisal of influenza epidemiological studies

resulted from the increased staff contact that ventilated infants require, in addition to the ventilator tubing acting as a potential route of infection.

Finally, the only known study to report control measures that were not confounded by influenza immunisation or use of antiviral prophylaxis, showed that cohorting of patients and staff (ie, the isolation of infected patients and their staff to isolation rooms and a separate ward, which were closed to new admissions during the outbreak), and droplet or contact control measures halted an outbreak of influenza in a neonatal intensive care unit.³⁹ No airborne precautions were used.

Discussion

Communicable viral respiratory diseases may be transmitted through various routes, including airborne, direct and indirect contact, and droplet transmission (panel). Droplet and contact transmission are traditionally defined as requiring close contact to occur, whereas airborne transmission may occur over much larger distances. As such, transmission of natural infection is seen over long (greater than 1 m between source and susceptible individual) and shorter (less than 1 m between source and susceptible individual, such as during a casual

conversation) distances, for those agents spread via the airborne route. In other words, a hallmark of airborne agents is that they should result in infections at long distance from the source.

Few, if any, respiratory viruses are thought to be exclusively transmitted via one route. To show the significance of a particular route, other potential confounding routes must be taken into account when designing experiments and drawing conclusions from epidemiological data. We recognise that the definitions used for various modes of transmission are likely to be overly simplistic, especially for droplet and airborne categories. There is no exact particle size cut-off at which pathogen transmission changes from exclusively droplet to airborne, or vice versa. Rather, as particle sizes decrease below 5 μm , droplet transmission presumably blends into airborne transmission.²⁸

In the case of influenza virus, constant mutation via antigenic shift and drift, and a wide, shifting host range also add an additional layer of complexity to the interpretation of the existing data: different strains of influenza clearly behave differently and this also depends on the species infected.⁴² For example, avian influenza strains are generally transmitted between birds via the faecal–oral route, yet transmission of avian strains to human beings is believed to occur mostly via direct contact between infected bird secretions and human respiratory mucosa.⁴³ Therefore, we do not believe that the results of animal transmission studies can necessarily be extrapolated to human beings, but rather, should provide guidance in developing appropriate human-based studies.

Perhaps the most urgent question from a planning perspective is whether influenza can be transmitted via the airborne route (ie, over long distances). Studies have shown that influenza viruses can survive in an artificially generated airborne aerosol for varying amounts of time, and these experimental aerosols can cause infection in both human beings and animals. However, we question whether these studies are relevant to the natural route of human transmission. The artificial aerosols studied were quite different from natural aerosols generated by coughing. The mean particle size of the aerosols manufactured in these studies was generally 5–6 μm or less, with less than 10% being larger than 8 μm .^{10,14,15,22,29} Other studies examining the particles produced during natural coughing have shown that more than 99·9% of the aerosol volume (and therefore presumably pathogens) is composed of particles with a diameter greater than 8 μm ,^{44,45} although initial particle size will decrease because of evaporation.⁴⁶ Thus, although natural coughing may produce particles of the correct size to remain suspended in the air, most of the particle volume remains too large and falls to the ground.⁴⁷ Additionally, three of the experimental studies required equipment to agitate the air to maintain the aerosol,^{11,14,15} thus creating an environment quite different from the natural state. Two

studies showed that human influenza strains decay at a faster rate than animal strains, suggesting that the choice of strain in these types of studies is indeed important.^{14,15}

Whereas mice, ferrets, and ponies can become infected from breathing aerosolised influenza in an enclosed space, and without the aid of a targeted airborne delivery system, we could not find published evidence of human infection resulting from aerosolised virus inhalation from the ambient air. We further note that a lower proportion infected (<20%) was reported among participants breathing aerosolised virus via a mask than that reported for most of the outbreak studies we reviewed. Furthermore, many of the infectious particles delivered by a mask may affect and infect the upper respiratory tract mucosae rather than distal alveoli. Finally, the observation that the required infectious dose of influenza is somewhat lower when delivered by artificial aerosol than via nasal inoculation,²⁸ is too far removed from natural infection to enable us to draw any conclusions on routes of transmission.

One human study compared natural and experimental illness by examining the clinical presentation and the results of pulmonary function testing of those with natural infection in comparison with those whose influenza was experimentally induced.³⁰ The investigators suggested that the more severe illness seen in the naturally infected versus intranasally infected participants may provide evidence for airborne transmission in the natural state. However, this study was substantially confounded by several factors: the naturally infected group was entirely composed of a subset of people with severe enough illness that they sought medical care; different influenza strains were used in the two groups; and the experimental group received a controlled inoculum whereas the inoculum received by the naturally infected was unknown.

Only one experimental study supported airborne transmission; however, it was done in ferrets rather than human beings. Andrewes and Glover¹⁸ showed that ferrets could become infected with influenza despite being separated by 2·5 m of ducting, including corners that would require infectious particles to follow the air currents. However, airflow was unilaterally directed through the ducts and the direction of airflow was from source towards the exposed animal. Although it is difficult to envision how transmission could have resulted through modes of transmission other than the air, care must be taken not to directly extrapolate animal-to-animal transmission models to human beings. Clearly, artificially aerosolised virus can infect human beings; however, we are unable to come to any conclusion about the plausibility and frequency of airborne transmission in the natural disease state from these studies, beyond stating that these studies do not rule it out.

The most often cited epidemiological study supporting airborne or long distance transmission of influenza involved an Alaskan Airlines flight with a non-

functioning ventilation system.³⁵ However, the investigators conceded that because of the free movement of passengers throughout the aircraft, close range transmission of influenza through droplet or direct contact could not be ruled out. A second aircraft outbreak study involving two planes with fully functioning ventilation systems also showed evidence of transmission.³⁶ Because proper ventilation is the most important factor to influence airborne transmission rates, if influenza is transmitted mainly by the airborne route, then one might have expected a very low proportion infected in this second study, given that the air exchange rate on the aircraft was similar to that required for an airborne isolation room.⁴⁸

Neither of the studies that compared influenza infection in different buildings or sections of the same facility appropriately accounted for all potential confounding factors such as the number of infectious index patients, patient allocation and characteristics, bed layout, presence of open windows, handwashing by staff and patients, length of stay, number of procedures, influenza immunisation status, and use of antiviral medications.³⁸ One study was further confounded by the fact that patients on the ward with the lowest attack rate also had more space allocated per patient (which would decrease transmission rates for diseases spread via contact or droplet routes), in addition to the most fresh air ventilation.³⁸ Individually, each of these factors has the potential to substantially influence the risk of exposure. Interestingly, the authors comment that the attack rates for the following influenza season were essentially identical between the four buildings. Furthermore, observation bias may have influenced the differences seen in the proportions of individuals infected between buildings or sections: of 15 refusals to provide a laboratory sample in one study, eight came from the building (one of four) with the lowest proportion infected. Finally, neither study reported the air exchange rates for the buildings or wings studied. We therefore believe that no conclusions about specific modes of influenza transmission can be made from the epidemiological studies cited above.

The remaining outbreak studies are more supportive of short-distance transmission, primarily via the droplet or contact route, as the predominant mode of influenza virus transmission. These studies provide evidence of spatial or temporal patterns of transmission (or both). For example, during an outbreak in a neonatal intensive care unit, Cunney and colleagues⁴⁰ interpreted the increased infection in twins as evidence that infected parents would have direct contact with both babies and would not necessarily wash their hands between each twin. Similarly, Awofeso and colleagues⁴¹ showed that, before becoming ill, each patient with influenza had been in close contact with an existing case. In none of these studies could a component of longer distance airborne transmission be entirely ruled out; however, we conclude

that this mode of transmission, if it did occur, was not epidemiologically important.

If influenza could be transmitted over long distances via the airborne route, then we would have expected to review studies citing evidence similar to that reported for the varicella zoster virus and *Mycobacterium tuberculosis*, both of which undergo known airborne transmission. Varicella DNA has been detected in air samples at distances ranging 1.2–5.5 m from varicella-infected patients' beds up to 24 h after discharge. In this study, viral DNA was also detected in rooms of patients without varicella on the same hospital ward.⁴⁹ Two epidemiological studies of varicella transmission were supplemented by airflow studies that showed directional airflow consistent with the spread of the illness.^{50,51} Both studies were able to rule out droplet or contact transmission because of the strict and immediate isolation of the index case on admission to the hospital. Interestingly, the airflow study of one report showed a substantially higher percentage of patients infected (90%) in a room that was at a marked negative pressure to the hallway because of an inoperative ventilation unit. By contrast, an operational ventilation unit impeded airflow into another equidistant room in which only 40% of patients were infected. With respect to *M tuberculosis*, studies by Riley and colleagues⁵² almost 50 years ago showed that a consistent proportion of guineapigs developed tuberculosis while breathing air vented from a human tuberculosis ward. They further showed that infection could be prevented by exposing the ducted air to ultraviolet irradiation.⁵²

Recently, a classification system for airborne transmission of pathogens has been suggested whereby transmission may be characterised as obligate, preferential, or opportunistic.⁵³ Obligate airborne transmission occurs with an infection that, under natural conditions, is initiated solely through aerosols deposited in the distal lung. Preferential airborne transmission refers to pathogens that may naturally initiate infection through multiple routes, but are predominantly transmitted by aerosols deposited in distal airways. Opportunistic airborne transmission occurs with infections that naturally and typically cause disease through other routes, but that can also initiate infection through the distal lung and may use fine-particle aerosols as an efficient means of propagating in favourable environments. We conclude that there is no evidence to support obligate or preferential airborne influenza transmission between human beings in the natural state. However, influenza may be transmitted by the airborne route under certain experimental conditions. This leaves open the possibility that influenza could be an opportunistic airborne pathogen, although this is not proven by the current literature.

Finally, influenza has long been thought to be transmitted by direct and indirect contact.^{54,55} Interestingly, although the virus can survive on surfaces in homes and

Search strategy and selection criteria

These are described in detail in the Methods section on page 2.

day-care centres,^{16,17} no study has shown that contact with contaminated surfaces could result in transmission. There is, however, substantial epidemiological evidence of transmission over short distances, although we cannot determine the relative significance of indirect contact in this transmission.

Conclusion

We conclude that natural influenza transmission in human beings occurs over short distances rather than over long distances. In turn, because it is well documented that airborne pathogens result in infection over long distances (in addition to close range), we conclude that natural influenza transmission occurs primarily via the droplet and contact routes. Although none of the reviewed studies could specifically rule out airborne transmission, we believe that the airborne route is neither the predominant mode of transmission, nor a frequent enough occurrence to be of significant concern when considering control measures for most clinical settings. Currently, no studies exist to help define the circumstances in which influenza might become opportunistically airborne, although aerosol-generating interventions such as bronchoalveolar lavage would be appropriate targets for future study. It may be reasonable to follow airborne precautions in such high-risk settings; however, this is not supported by the literature.

In the current scenario in which unanswered questions remain about the role aerosols may or may not have in the natural transmission of influenza, it remains essential to keep in mind the main goal, which is to reasonably minimise risk of transmission of influenza infection in the health-care setting. A study has called for the routine use of N95 respirators (approved by US National Institute of Occupational Health and Safety) during a human influenza pandemic.⁵⁶ This approach is complicated by a number of factors. First, under occupational health and safety legislation such as that in our Canadian province,⁵⁷ N95 respirators and those with higher filtration require fit testing. Once an individual has been fit tested, they must use only the brand and size of respirator for which they have been certified. During a pandemic, supplies may be limited and supply chains may become disrupted; hence the availability of the appropriate brand and size of respirator for each health-care worker will be difficult to guarantee. Second, the sheer number of N95 respirators marketed will make the stockpiling of appropriate numbers logistically difficult, if not impossible. Current Canadian and other national pandemic influenza plans call for the use of droplet and contact precautions by health-care workers and the stockpiling of this equipment is underway in many countries.²⁻⁴ Third, the reproducibility of fit testing over time has been questioned.⁵⁸ Fourth, prolonged use of N95 respirators has been shown to cause headaches,⁵⁹ facial discomfort,⁶⁰ and may result in hypoxia.⁶¹ Therefore, we seriously question whether poor compliance would

negate any potential benefit that might be gained from their use. Regardless of which precautions are taken by health-care workers, transmission during a pandemic is believed to be inevitable because of the sheer number of exposures, and because health-care workers can become infected in community settings in which protective equipment is not used.²

Other strategies warranting further consideration and study, and which may better achieve the goal of reasonably minimising risk in health-care settings than the use of airborne precautions, include the broad use of antiviral prophylaxis. However, this too would require early planning and the development of stockpiles before a pandemic occurs.^{62,63}

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Conflicts of interest

We declare that we have no conflicts of interest.

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