Does Influenza Transmission Occur from Asymptomatic Infection or Prior to Symptom Onset?

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SYNOPSIS

A better understanding of transmission dynamics is essential in influenza pandemic planning. If a substantial proportion of transmissions were to occur during the presymptomatic phase or from asymptomatic individuals, then infection control measures such as contact tracing and quarantine of exposures would be of limited value. Infectiousness has been inferred based on the presence of influenza in the upper respiratory tract rather than from transmission experiments. Although asymptomatic individuals may shed influenza virus, studies have not determined if such people effectively transmit influenza.

We performed a systematic review of published studies describing the relationship between viral shedding and disease transmission. Based on the available literature, we found that there is scant, if any, evidence that asymptomatic or presymptomatic individuals play an important role in influenza transmission. As such, recent articles concerning pandemic planning, some using transmission modeling, may have overestimated the effect of presymptomatic or asymptomatic influenza transmission. More definitive transmission studies are sorely needed.

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Public health measures used to control outbreaks involve isolation of symptomatic individuals and quarantine of their contacts. Such interventions depend on early recognition of disease symptoms, and their success is limited by transmission that occurs prior to symptom onset, transmission from asymptomatic infection, and the inherent transmissibility of an infectious agent.[1–3]

One in three influenza-infected individuals is asymptomatic.[4] Mathematic models of influenza transmission and control have included presymptomatic and asymptomatic individuals.[2,4–7] The proportion of transmission by asymptomatic individuals, defined as Theta (T) in transmission models, is assumed to be one-third to one-half that of influenza-infected symptomatic individuals.[2,8,9] Studies that estimate the expected reduction in primary attack rates for different household-based interventions (the combination of home quarantine, isolation of cases outside the home, and targeted prophylactic use of antimicrobials to household contacts) have shown that the reduction in initial attack rates will be affected by the population compliance rate (p_c) and the proportion of transmission from asymptomatic or presymptomatic individuals (T).[6] However, supportive evidence for asymptomatic influenza transmission is scant.[10,11] If T is small or nonexistent, quarantine measures targeting infectiousness during the incubation period will be ineffective, whereas individual-level isolation, namely isolation of infected people and contact tracing, will be an effective control measure. Because such models are used to formulate national and international policies for mitigation of influenza spread during a pandemic, determining the true risk of transmission from presymptomatic and asymptomatic individuals is of paramount importance.

METHODS

We performed a systematic review to ascertain the relationship between viral shedding and disease transmission. A literature search was carried out using the PubMed database with the keywords "influenza" and "shedding" (all fields), "symptoms" (all fields), "asymptomatic" (all fields), or "transmission" (all fields). We also reviewed the bibliographies of published studies to find additional, related articles. We limited our search to English-language articles.

RESULTS

Our understanding of influenza transmission reflects data derived from animal studies,[12–16] human studies with experimental influenza virus infection, inoculation experiments,[4,17,18] vaccine and antiviral drug efficacy studies,[17,19,20] household cohort studies,[21–25] and observations during outbreaks.[26]

Animal studies

In a guinea pig model, environmental conditions were found to impact the results of transmission experiments whereby a cool ambient environment with low humidity was more conducive to influenza transmission.[12] In other animal studies, mice (i.e., infector mice) were infected with influenza virus by aerosol exposure. Immediately afterward, infector mice were removed from the aerosol chamber and placed in cages with four successive groups of susceptible mice for 24-hour increments.[13,14] After the first group of susceptible mice was exposed to an infector mouse for 24 hours, the susceptible mice were removed from the cage and a second group of susceptible mice was placed in the same cage, and so on.

After each 24-hour exposure period, susceptible mice were quarantined. Viral titers were then measured in various tissues. Although influenza virus was detected by throat swabs in 56% of the infector mice within 24 hours of inoculation, only three of 80 mice (4%) in the susceptible group exposed during the first 24-hour time interval acquired influenza. Infector mice were found to transmit influenza almost exclusively during the second 24-hour interval after exposure to the aerosol chamber, but this did not correlate with a peak in the viral titer detected in any of four sites of the respiratory tract sampled in the infector mice. Thus, transmission was ineffective during the first 24 hours despite evidence of viral shedding in more than half of the mice at that time, and shedding alone did not correlate with the likelihood of influenza transmission. We can only speculate that effective transmission in this experiment reflected the presence of virus in the respiratory tract of mice at a time when their symptoms were most conducive to disease transmission, which occurred during the second 24-hour interval after exposure.

The mouse model has been extensively criticized and is not considered to be ideal to study influenza transmission, as mice are not a natural host for the disease, they do not develop symptoms that can be monitored, nor do they consistently transmit infection from one animal to another.[15] Thus, paucity of information regarding influenza transmission can be attributed, in part, to the lack of a more convenient animal model. Recently, ferrets have been used to investigate influenza transmission.[16] In ferrets, the course of infection and resultant disease symptoms closely resemble influenza illness in humans: ferrets with influenza infection develop anorexia, weight loss,

fever, sneezing, and nasal symptoms. Hence, ferrets would be excellent models for studying presymptomatic or asymptomatic transmission.

Human studies

Experimental influenza virus infection. Rhinorrhea, coughing, and sneezing facilitate transmission of respiratory viruses; however, viral shedding may not correlate with nasal symptoms. In two studies,[17,18] shedding was greater in symptomatic than in asymptomatic individuals, and for symptomatic patients, shedding correlated with severity of illness. In an expansive review of experimental influenza infection of healthy volunteers, the viral shedding increased during the first day after inoculation, consistently peaked on the second day, and lasted less than five days. Viral shedding preceded clinical illness by one day. However, the authors found limited information on viral shedding in the asymptomatic volunteer group, and the association between shedding and transmission was not examined.[4]

Vaccine and antiviral drug efficacy studies. In vaccine studies, the amount of viral shedding and daily fever score were strongly correlated.[17,19] Similarly, antiviral drug efficacy studies showed peak shedding early in the course of illness. Shedding correlated with signs and symptoms of influenza infection. However, presymptomatic shedding was not examined, nor was influenza transmission.[20]

Household cohort studies. Household cohort studies have demonstrated that low levels of viral shedding occur one to two days prior to symptom onset, but peak shedding correlates with symptoms.[21–25] These studies did not assess whether or not asymptomatic people transmitted influenza.

Outbreak investigations. One observational study implicated influenza transmission prior to onset of respiratory symptoms.[26] An influenza-like illness developed in 16 of 26 adults who bagged fertilizer in an enclosed setting for eight hours; three of the 26 adults developed a mild, cold-like illness. The symptoms developed within 48 hours of this activity. The probable index patient felt unwell during work but reportedly had no respiratory complaints at that time. An influenza-like illness began six hours after he finished work. Influenza virus was isolated from two of the symptomatic contacts. It is unclear if influenza was isolated from the suspected index case. Thus, it is unknown if the suspected index case transmitted influenza to the others, or if transmission occurred from community exposure. The group also shared drinking bottles, which may have facilitated transmission.

DISCUSSION

Presymptomatic transmission of influenza has been inferred based on the presence of the virus in the upper respiratory tract rather than from appropriate transmission experiments. This is troubling because our review of the literature does not support significant influenza transmission based on positive nasopharyngeal cultures in the absence of symptoms. Asymptomatic individuals may shed influenza virus, but studies have not conclusively determined if such people effectively transmit influenza.

In community settings, influenza transmission was previously believed to occur predominantly by large, virus-laden respiratory droplets (i.e., particles >5μm in diameter) expelled during sneezing and coughing.[27,28] However, individuals inherently differ in their ability to spread respiratory droplets,[15] and in some people, mouth breathing may produce larger quantities of airborne droplets than nose breathing, talking, or coughing.[29] Some people exhale large quantities of viral particles that can be detected during quiet breathing. For example, a study of 11 subjects that quantified small droplets of airway lining fluid exhaled during normal breathing found that the exhaled bioaerosol varied from one to >10,000 particles/liter.[30] Interestingly, 98% of all particles were from six of 11 subjects characterized as "high producers." Such individual differences may account for inconsistent and confounding results observed in some studies.[28] In a recent study of influenza-infected individuals, most of whom had multiple symptoms, fine-particle aerosols (i.e., mainly <1μm in diameter) were exhaled during tidal breathing in 33% of such people.[31] As in the previously cited study,[28] half of the influenza-infected individuals shedding virus during tidal breathing were high-particle producers. These findings suggest that small-particle aerosols may play a greater role in influenza transmission than previously recognized. However, the extent to which viral-laden aerosols are generated during tidal breathing in asymptomatic or presymptomatic, influenza-infected individuals is unclear.

Most viruses that cause respiratory tract infections, including influenza, infect the epithelium of the upper airway via exposure to infectious respiratory droplets or by self-inoculation from contaminated hands after contact with infectious secretions on environmental surfaces. Regarding the latter route of transmission, influenza virus has been isolated from more than half of the fomites tested in homes and day care centers during influenza season.[32] In addition, influenza transmission has been documented to occur from porous and nonporous surfaces to the hands of volunteers in large enough quantities to cause disease.[33] These data

support the feasibility of influenza spread by indirect contact, but documented human infection resulting from contact with contaminated objects has not been adequately investigated.

CONCLUSION

A better understanding of transmission dynamics is essential in influenza pandemic planning. If a substantial proportion of transmission were to occur during the presymptomatic phase or from asymptomatic individuals, then infection control measures such as contact tracing and quarantine of exposures will be of limited value, in addition to constraints based on the short serial interval for influenza transmission. However, we have found limited evidence to suggest the importance of such transmission. The role of asymptomatic or presymptomatic influenza-infected individuals in disease transmission may have been overestimated in recent articles dealing with pandemic planning. More definitive influenza transmission studies are needed.

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