Journal of Infection (2008) 57, 361—373

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BRITISH INFECTION SOCIETY

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REVIEW

Inactivation of influenza A viruses in the environment and modes of transmission: A critical review

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Accepted 27 August 2008
Available online 9 October 2008

KEYWORDS
Influenza A virus;
Virus inactivation;
Environment;
Transmission;
Aerosols;
Fomite

Summary *Objectives:* The relative importance of airborne, droplet and contact transmission of influenza A virus and the efficiency of control measures depends among other factors on the inactivation of viruses in different environmental media.
Methods: We systematically review available information on the environmental inactivation of influenza A viruses and employ information on infectious dose and results from mathematical models to assess transmission modes.
Results: Daily inactivation rate constants differ by several orders of magnitude: on inanimate surfaces and in aerosols daily inactivation rates are in the order of $1-10^2$, on hands in the order of 10^3. Influenza virus can survive in aerosols for several hours, on hands for a few minutes. Nasal infectious dose of influenza A is several orders of magnitude larger than airborne infectious dose.
Conclusions: The airborne route is a potentially important transmission pathway for influenza in indoor environments. The importance of droplet transmission has to be reassessed. Contact transmission can be limited by fast inactivation of influenza virus on hands and is more so than airborne transmission dependent on behavioral parameters. However, the potentially large inocula deposited in the environment through sneezing and the protective effect of nasal mucus on virus survival could make contact transmission a key transmission mode.

Introduction

Three different, mutually non-exclusive modes of influenza transmission have been identified and discussed so far: droplet, airborne and contact transmission.[1–4] Droplet transmission requires the infectious case to directly spray

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0163-4453/$34
doi:10.1016/j.jinf.2008.08.013

large droplets by coughing or sneezing onto conjunctiva or mucous membranes of a susceptible host. Airborne transmission through droplet nuclei does not require face-to-face contact with the infectious case. Droplet nuclei settle from the air slowly, are respirable and can thus transmit the virus directly into the alveolar region. Contact transmission occurs either indirectly through contact with secretions on fomites or directly such as through physical touch between an infected individual and a susceptible host.[1,5] We need to emphasize that there is no unique and generally agreed-upon classification of airborne droplets, for example, concerning the aerodynamic diameter d_a which defines the cut-off size between droplet nuclei and large droplets. Definitions and classifications differ between medicine and aerosol science and depend on explanatory interest. When evaluating airborne transmission, a cut-off point of 5 μm is commonly chosen.[1] We, however, propose a (post-evaporation) value of 10 μm because droplets of this size can remain airborne for several minutes. The settling time for a 10-μm particle from a height of 1.5 m is 491 s; the settling time then drops rapidly with increasing particle size.[6] In the following we only use the terms droplet nuclei and large droplets; Table 1 and Fig. 1 summarize the concepts, terms and interrelationships important for the description of transmission modes.

Which of the three transmission modes is responsible for most influenza infections remains highly controversial.[3,4,7–12] Especially the importance of the airborne pathway via droplet nuclei has proved to be contentious — despite often repeated statements such as ''Influenza virus is readily transmitted by aerosols (...)''[13] (p. 1278) and the obvious importance of knowing the significance of this transmission mode for implementing efficient non-pharmaceutical control measures.[14–16] Should, for example, the use of face masks be recommended during a pandemic, when a vaccine is not yet available, on the basis of what we know or do not know about airborne or droplet transmission? Is airborne transmission perhaps only important indoors, but not outdoors, where virus removal by dilution, air circulation and also virus inactivation might be higher? How can airborne infections efficiently be controlled in health care settings?[17–21]

One factor contributing to the relative importance of each of the three transmission modes is the inactivation of influenza A viruses in different environmental media. Sometimes, viruses in transmission are described as being ''outside of their natural habitat''[17] (p. 457); transmission, however, is an integral part of the ''life'' cycle of viruses and thus shaped by natural selection.[22] A full understanding of transmission modes requires a comprehensive understanding of mechanisms on several different levels of organization, from virion structure to aspects of human behavior and social organization. We consider these latter aspects if necessary, but focus on the characteristics of transport medium and their consequences for virus inactivation. The empirical study of these issues is never easy, but especially challenging for aerosols. The size distribution of respiratory aerosols, their size changes after expulsion[2] and subsequent inhalation,[23] the pathogen concentration and the mechanisms of virus inactivation are factors that are very difficult to study empirically. Environmental persistence is key parameter, because it can place strict limits on the impact of a transmission pathway. Despite its probable relevance, and possibly because of the empirical challenges, the issue of environmental persistence and mode of transmission of influenza A has remained a comparatively neglected topic. Charles V. Chapin claimed in 1910 that communicable respiratory infections are transmitted by means of large droplets over short distances or through contact with contaminated surfaces.[24] This claim has remained dominant ever since. The paradigm of droplet and contact transmission experienced a temporary challenge through the pioneering work of William F. Wells, who produced experimental evidence for the existence of droplet nuclei as a means of airborne transmission of respiratory diseases. The airborne route of infection and influenza virus inactivation in aerosols was quite intensely researched from the late 1930s to the early 1980s,[25–44] received some still contested epidemiological support,[45] but then failed to attract noteworthy attention for many years. Outside the community of influenza researchers the topic of airborne transmission and virus inactivation remained of some interest[46]; a review concluded that airborne transmission is possible for numerous types of viruses.[47] In influenza research, the airborne route only recently has regained significant and controversial interest.[3,4,48,49] There appears to be agreement that airborne transmission is at least possible, but there is strong disagreement about importance. There are a number of reasons for this renewed attention to the airborne transmission route, for example the need to consider and develop non-pharmaceutical interventions in case of a pandemic[14,15] or emerging diseases such as SARS where the transmission mode remained controversial and uncertain for some time and it subsequently turned out that airborne transmission was feasible.[50] These developments, and the threat of bioterrorism,[51] have reopened and revitalized the debate about the transmission modes of influenza.

Environmental inactivation of influenza A virus also plays an essential role in other controversial issues. How does influenza A persist between seasonal epidemics?[52–55] Is there continuous serial, person-to-person transmission or do they survive extended periods in the environment? The threat of highly pathogenic avian H5N1 to jump permanently to human hosts has led to the consideration of a transmission

Table 1 Definitions of terms

Aerodynamic diameter d_a	The diameter of a sphere with unit density that has aerodynamic behavior identical to that of the particle in question
Inhalable (inspirable) large droplets	Airborne particles that enter the body through the nose and/or mouth during breathing
Respirable droplet nuclei	The fraction of inhaled particles that penetrates to the alveolar region of the lung and are available for deposition