Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Virology

Drivers of airborne human-to-human pathogen transmission

Sander Herfst[1], Michael Böhringer[2], Basel Karo[3,4], Philip Lawrence[5,6], Nicola S Lewis[7], Michael J Mina[8], Charles J Russell[9], John Steel[10], Rik L de Swart[1] and Christian Menge[11]

Airborne pathogens — either transmitted via aerosol or droplets — include a wide variety of highly infectious and dangerous microbes such as variola virus, measles virus, influenza A viruses, *Mycobacterium tuberculosis*, *Streptococcus pneumoniae*, and *Bordetella pertussis*. Emerging zoonotic pathogens, for example, MERS coronavirus, avian influenza viruses, Coxiella, and Francisella, would have pandemic potential were they to acquire efficient human-to-human transmissibility. Here, we synthesize insights from microbiological, medical, social, and economic sciences to provide known mechanisms of aerosolized transmissibility and identify knowledge gaps that limit emergency preparedness plans. In particular, we propose a framework of drivers facilitating human-to-human transmission with the airspace between individuals as an intermediate stage. The model is expected to enhance identification and risk assessment of novel pathogens.

Addresses
[1] Department of Viroscience, Postgraduate School of Molecular Medicine, Erasmus MC, Wytemaweg 80, 3015 CN Rotterdam, The Netherlands
[2] Friedrich-Loeffler-Institut, Institute of Bacterial Infections and Zoonoses, Naumburger Str. 96a, 07743 Jena, Germany
[3] Robert Koch Institut, Department for Infectious Disease Epidemiology, Seestr. 10, 13353 Berlin, Germany
[4] PhD Programme ''Epidemiology'', Braunschweig-Hannover, Germany
[5] Université de Lyon, UMRS 449, Laboratoire de Biologie Générale, Université Catholique de Lyon – EPHE, Lyon 69288, France
[6] Molecular Basis of Viral Pathogenicity, International Centre for Research in Infectiology (CIRI), INSERM U1111 – CNRS UMR5308, Université Lyon 1, Ecole Normale Supérieure de Lyon, Lyon 69007, France
[7] Centre for Pathogen Evolution, Department of Zoology, University of Cambridge, Downing Street, Cambridge, United Kingdom
[8] Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ 08544, USA
[9] Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, TN 38105, USA
[10] Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta, GA 30322, USA
[11] Friedrich-Loeffler-Institut, Institute of Molecular Pathogenesis, Naumburger Str. 96a, 07743 Jena, Germany

Corresponding author: Herfst, Sander (s.herfst@erasmusmc.nl)

Current Opinion in Virology 2017, **22**:22–29

This review comes from a themed issue on **Emerging viruses: intraspecies transmission**

Edited by **Ron A.M Fouchier** and **Lin-Fa Wang**

For a complete overview see the Issue and the Editorial

Available online 2nd December 2016

http://dx.doi.org/10.1016/j.coviro.2016.11.006

Introduction

The horror of airborne infectious diseases subsided substantially in the 20th century in developed nations, largely due to implementation of hygiene practices and the development of countermeasures such as vaccination and antimicrobials. The recent emergence of zoonotic pathogens such as avian influenza A viruses (e.g. H5N1 and H7N9) and coronaviruses (CoV) (i.e. SARS CoV (severe acute respiratory syndrome) and MERS CoV (Middle East respiratory syndrome)) raises the specter of future pandemics with unprecedented health and economic impacts if these pathogens gain the ability to spread efficiently between humans via the airborne route. While cross-species barriers have helped avoid a human pandemic with highly pathogenic avian influenza A (HPAI) viruses, a limited number of mutations in circulating avian H5N1 viruses would be needed for the acquisition of airborne transmissibility in mammals [1•]. A global pandemic by SARS CoV was averted largely by fast identification, rapid surveillance and effective quarantine practices. However, not all emerging pathogens can be contained due to a delay in initial detection, an inability to properly assess pandemic risk, or an inability to contain an outbreak at the point of origin. Before 2009, widely circulating H1N1 swine viruses were largely thought to pose little pandemic risk but, despite early attempts to limit spread, pH1N1 caused the first influenza virus pandemic of the 21st century. Implementation of suitable countermeasures is hampered by our limited capability to anticipate the sequence of events following

the initial detection of a novel microorganism in an animal or human host. In the immediate future, the occurrence of (i.e. frequency of spill-over events from an animal to the human population), the detection of (i.e. diagnostic capabilities), and the awareness for (i.e. likelihood of public health services to recognize) novel epidemic agents will likely increase qualitatively and quantitatively. Updating of emergency preparedness plans in an evidence-guided process requires an interdisciplinary concept of research and public health efforts taking into account the multifactorial nature of the problem to aid policy formulation [2]. Here we build on a conceptual framework for the classification of drivers of human exposure to animal pathogens [3••] and suggest a framework of drivers determining the efficiency of human-to-human transmission involving the airspace.

Circle of transmission events

The airborne transmission of pathogens occurs through 'aerosol' and 'droplet' means [4,5••]. In a strict sense, *airborne transmission* refers to aerosols (≤5 μm) that can spread over distances greater than 1 m, while *droplet transmission* is defined as the transfer of large-particle droplets (>5 μm) over a shorter distance [5••]. Here, we consider airborne transmission of infectious agents in a broader sense as any transmission through the air which consists of four steps (Figure 1): Firstly, the pathogen is associated with either liquid droplets/aerosols or dust particles when traveling directly from donor to recipient, but may also be deposited on a surface and re-emerge into the air later; secondly, the pathogen is deposited in the recipient, usually by inhalation, resulting in infection of the respiratory tract; thirdly, the pathogen is amplified, either in the respiratory tract or in peripheral tissues; and finally, the pathogen is emergent at the site of shedding (in most cases the upper respiratory tract) in sufficient loads and capable of expulsion. In the process of transmission, the recipient becomes a donor when microbial replication and subsequent pathophysiological events in the host result in release of the pathogen.

Drivers impacting on movement of pathogens through the air

Airborne transmission of microbes can follow different aerodynamic principles, and some microorganisms are suspected or proven to spread by more than one route [4]. Moreover, the mode of transmission and anisotropic delivery of a pathogen into the recipient contributes to disease severity [6,7]. There are no substantive differences between droplet-size distribution for expulsive methods like sneezing, cough with mouth closed, cough with mouth open, and speaking loudly one hundred words [8–10]; however, the number of respiratory droplets that likely contain pathogens can differ [9]. After expulsion, successful transmission requires that the pathogen remains infectious throughout airborne movement, with or without an intervening deposition event (Figure 1). Drivers influencing the success of such a process are those that define the chemico-physical properties of both the air mass and the vehicle or carrier, including temperature, ultraviolet (UV) radiation, relative (RH) and absolute humidity, and air ventilation (inside) or air movement (outside) [9]. Their interplay ultimately determines pathogen movement and stability [11–13]. Pathogen survival is also influenced by pathogen structure, for example, enveloped viruses are less stable outside the host than non-enveloped viruses [14]. Among *Chlamydia* (*Ch.*) *pneumoniae*, *Ch. trachomatis* LGV2, *Streptococcus* (*S.*) *pneumoniae*, *S. faecalis*, *Klebsiella pneumoniae*, and cytomegalovirus, the survival of *Ch. pneumoniae* (and *S. faecalis*) in aerosols was superior [15]. Variation in RH might influence not only environmental stability of the pathogen but also the droplet size [16] which in turn defines deposition rate [16,17]. Eighty percent of droplets emitted from a cough deposit within 10 min, and highest deposition rates for all droplet-nuclei sizes range within 1 m horizontal distance [17]. Pathogens like influenza virus can persist in the environment for hours to days and have been found on surfaces in healthcare settings [18–21]. UV radiation is the major inactivating factor for influenza viruses in the outdoor environment (reviewed in [22]).

Drivers impacting on the infection of the recipient

Pathogen-containing large particles (>6 μm) deposit predominantly in the upper airway, medium-sized particles (2–6 μm) mainly in central and small airways, and small particles (<2 μm) predominantly in the alveolar region of the lungs [23]. In general, airborne pathogens tend to have a relatively low infectious dose 50% (ID_{50}) value. At any specific site of deposition within a host, ID_{50} of a pathogen is determined by factors such as local immune responses and the cellular and tissue tropism defined by distribution of receptors and/or adherence factors, tissue temperature, pH, polymerase activity of the pathogen, and activating proteases. Co-infections may alter immune responses and factors that govern tropism.

Drivers impacting on pathogen amplification in the host

Pathogens amplify either at the site of initial deposition in the respiratory tract or in peripheral tissues. For influenza virus or human respiratory syncytial virus, this is the site of initial entry whilst other pathogens have either distinct secondary amplification sites or replicate both locally and systemically, for example, Measles virus (MeV), Nipah virus and *Mycobacterium* (*M.*) *tuberculosis* (Figure 1).

Microorganisms often damage host tissue through the release of toxins and toxic metabolites, as a direct result of replication, or as a consequence of activation and infiltration of immune cells [24••]. This may allow the pathogen to spread in the body and replicate to sufficient numbers to favor onward transmission. Self-assembly in