COVER SHEET

DROPLET FATE IN INDOOR ENVIRONMENTS, OR CAN WE PREVENT THE SPREAD OF INFECTION?

ABSTRACT

When considering how people are infected and what can be done to prevent the infections, answers from many disciplines are sought: microbiology, epidemiology, medicine, engineering and physics. There are many pathways to infection spread, and among the most significant, from an epidemiological point of view, is airborne transport. Microorganisms can become airborne when droplets are generated during speech, coughing, sneezing, vomiting, or atomisation of faeces during sewage removal. The fate of the droplets is governed by the physical principles of transport, with droplet size being the most important factor affecting their dispersion, deposition on surfaces and determining the survival of microorganisms within the droplets. In addition physical characteristics of the indoor environment as well as the design and operation of building ventilation systems are of critical importance. Do we understand the mechanisms of infection spread and can we quantify the droplet dynamics under various indoor conditions? Unfortunately no, as this aspect of infection spread has attracted surprisingly little scientific interest. However, investigations of numerous cases in which a large number of people were infected show how critical the physics of microorganism spread can be. This paper reviews the state of knowledge regarding mechanisms of droplet spread and solutions available to minimize the spread and prevent infections.

KEYWORDS

Infectious droplets, droplet transport, infection spread, airborne virus particles.

PRACTICAL IMPLICATIONS

Every day tens of millions of people worldwide suffer from viral infections of different severity at immense economic cost. There is, however, only minimal understanding of the dynamics of virus laden aerosols, and so the ability to control and prevent virus spread is severely reduced, as was clearly demonstrated during the recent SARS epidemic. This paper proposes the direction to significantly advance fundamental and applied knowledge on the pathways of viral infection spread in indoor atmospheric systems, through a comprehensive multidisciplinary approach and application of state of the art scientific methods. Knowledge gained will have the potential to bring unprecedented economical gains worldwide by minimizing/reducing the spread of disease.

INTRODUCTION

The last few decades have witnessed an unprecedented increase in theoretical and applied knowledge in all areas of human endeavour. The tools that are now available to probe nature and its laws, not all that long ago would have been considered to belong to the realm of science fiction. Many questions from previous generations of scientists have been answered, opening new chapters in scientific progress and enabling new questions to emerge. Therefore, it is quite astonishing to encounter exactly the same questions asked decades ago in an area that is important not only to well being, but also to the survival of people worldwide: infection spread.

Viruses have been identified as the most common cause of infectious diseases acquired within indoor environments, in particular those causing respiratory and gastrointestinal infection. Among the most common types causing respiratory infections are influenza viruses, rhinoviruses, coronaviruses, respiratory syncytial viruses (RSVs) and parainfluenza viruses (PIVs); while those responsible for gastrointestinal infections include rotavirus, astrovirus, Norwalk-like viruses (NLVs) and other caliciviruses. Some of these infections are very widely spread but are not severe, such as the common cold; while others are relatively more severe, like influenza. Economic losses due to these and a wide range of other types of viral infections are astronomic and include the costs of medical treatment of the infected people, costs of lost income due to inability to work, and finally costs of decreased productivity of those who are infected, yet continue to work.

There are many pathways of virus transmission, the main ones include:

Human-human transmission

- Direct contact with an infected person
- Indirect contact, through an intermediate object, primarily via hands or fomites

Airborne transmission

- Via droplet contact spread and airborne spread of droplet residue, skin flakes and fungal spores. Aerosol droplets are generated and released during speech, coughing sneezing, vomiting, or aerosolation of faeces during sewage removal and treatment.

Other

- Endogenous infection
- Common vehicle and vector spread

The degree of hazard created by biological contaminants such as viruses in indoor environments is controlled by a number of factors including: (1) the type of virus and potential health effects it causes; (2) mode of exit from the body; (3) concentration levels, (4) size distribution of aerosol containing the virus; (5) physical characteristics of the environment (temperature, humidity, oxygenation, UV light, suspension medium etc); (6) air circulation pattern; and (7) operation of heating, ventilation and air conditioning system.

Advances in genetic science have lead to significant progress in the understanding of the epidemiology, pathogenesis and treatment of viral infections once a virus particle is brought in contact with a suitable human host. This was demonstrated during the severe acute respiratory syndrome (SARS) outbreak in 2002/2003, when the genetic code of the new virus was described within one month of its first isolation and the results of research focused on identification of etiological agents of this outbreak were already published while the SARS outbreak was ongoing However, one area of critical importance in the transmission of viral diseases, which has attracted much less scientific focus, is the science of virus transport from the point of release to the host organism. The dynamics of virus carriage and survival in aerosol droplets, the role of environmental factors and ventilation are poorly understood. As a consequence, understanding of the mechanisms of virus spread is less than basic and so is the ability to control and prevent that spread. This was dramatically illustrated during the recent epidemic of SARS, where it was not possible to pinpoint exactly how the virus was spreading until much later, when retrospective studies were able to suggest the routes of virus transport.

The thrust of this paper is to show that deepening the knowledge and developing understanding of the physics and microbiology of virus transport and their survival in the air is necessary to limit or prevent viral spread, which will contribute to the control of infectious diseases in health care settings, in public places and in indoor and outdoor environments. This in turn has the potential to bring unprecedented economical gains worldwide.

AEROSOLS AND BIOAEROSOLS IN INDOOR AIR

Liquid and solid airborne particles – aerosol – in indoor air originate from many indoor and outdoor sources. Particles may differ in size, shape, chemical composition and biological composition. Particle size is the most important parameter affecting particle fate during transport and it is also significant in affecting their biological properties. Primarily, particle size is a consequence of the process that led to its generation, and thus it is also dependent on the source. Particles below 1μm, submicrometer particles, are generated mainly from combustion, gas to particle conversion, nucleation or photochemical processes; while larger airborne particles, up to about 100 μm, result mainly from mechanical processes such as mineral and material processing, breaking and wear of material and dust resuspension. Particles in the submicrometer range typically contain a mixture of components including soot, acid condensates, sulfates and nitrates, as well as trace metals and other toxins. Coarse particles largely contain earth crustal elements and compounds. Infectious biological aerosols in indoor environment include: viruses (influenza, measles, varicella (chickenpox)); bacteria (Chlamydia (psittacosis), Mycobacterium (tuberculosis), Legionella (legionnaire's disease)); and fungi (Aspergillus (aspergillosis)). The sizes of these

different types of biological aerosols vary and can be broadly classified as follows: viruses from 0.02 to 0.3 μm, bacteria from 0.5 to 10 μm, and fungi from 0.5 to 30 μm. For example, an individual SARS coronavirus ranges from 0.075 – 0.160 μm in diameter, and is a spherical virion. An influenza virus is of a similar size, and is also spherical. Infectious bioaerosol particles may exit as (1) single bacterial cells or spores, fungal spores or viruses; (2) aggregates of several single cells, spores, or viruses (3) biological material carried by other non-biological particles.

From the above it could be inferred that the movement and fate of viruses in the air will be driven by what drives the movement of submicrometer particles. However, the situation is more complicated and also depends on: (1) how viruses are introduced into the air and (2) how they are equipped to respond to environmental challenges, primarily moisture and temperature conditions. In relation to the former, atomisation is one of the key mechanisms that needs to be considered, while to the latter, presence or lack of the 'envelope' is of significance to virus response to moisture conditions. An envelope is a lipid membrane, which surrounds capsid in some viruses, as opposed to 'naked' viruses without a membrane. These two aspects are discussed in more detail below.

ATOMISATION, A MECHANISM FOR DROPLET FORMATION

Atomization is a process of producing droplets or 'sprays' by dispersing bulk liquid phase into gas phase eg (Sirignano 1999). The basis of so called 'air-jet' atomization is the interaction of a high velocity air stream with that of a relatively slow moving flow of liquid. The physical forces governing the process are surface tension and viscosity versus aerodynamic forces. Surface tension has a consolidating influence, which opposes extension of the surface ("stretching of the particle"), while liquid viscosity exerts a stabilizing influence by opposing any change in the shape of droplets as they are produced. Surface tension will tend to minimize the droplet surface area, given its volume, resulting in a spherical shape for sufficiently small droplets. Aerodynamic forces acting on the liquid surface promote disruption by exerting force on the bulk liquid. Primary atomization refers to the break-up process affected only by internal forces, while secondary atomization includes the action of external aerodynamic forces. These forces on a droplet depend on its size in a functional manner, different from the dependence of droplet mass on the size. As a result, smaller droplets undergo more rapid acceleration or deceleration than larger droplets. The final spray depends not only on the primary droplets produced, but also on the extent to which these droplets are further disintegrated. In addition, of importance are processes such as vaporization and condensation; in particular, heating and vaporization times are shorter for smaller droplets. The aerosol resulting from atomisation may then be modified both physically and chemically by a variety of mechanisms and removed from the air. These processes include: gravitational deposition (large particles), shrinking by evaporation, growth (if they are hygroscopic), coagulating with other airborne particles, depositing on surfaces.

In the natural environment there are many processes in which liquid (mainly water) atomisation occurs, including waterfalls, atomization of rain droplets, and atomization of water from the surface of the ocean by the action of wind on the wave crest and by breaking of the waves. The evaporation of water from the airborne ocean droplets results in aerosol particles composed of the salts and other materials originally contained in the seawater.

In a laboratory setting, droplets can be produced by devices such as atomizers or nebulizers. Size distribution of droplets generated in a relatively simple process, like that occurring in Collison Atomizer for example, can be predicted theoretically, as can the size distribution of the droplet residue that would result from drying of the individual droplets. *However, for most liquid injection systems only empirical methods exist to represent droplet distribution and the distribution cannot be predicted from a first principles approach (Sirignano 1999) because a general theory that describes the formation and break-up of droplets during atomisation process has not been developed.* Only for certain types of applications (such as fuel injectors), is an understanding of the process of atomization being gradually developed (Hickey 1996).

FORMATION OF INFECTIOUS BIOAEROSOLS BY HUMANS AND AS A RESULT OF THEIR ACTIVITIES

Humans and their activities are linked to a number of processes resulting in introduction of droplets with infectious content into the indoor air, including:

- Expiratory activities of humans: human breathing, speaking, coughing, sneezing, etc;
- Showering, using tap water (atomisation of infectious bioaerosols, particularly bacteria, present in the water or in the local plumbing);
- Sewage aerosolation from toilets and its transport in building downpipe systems;
- Wet-cleaning of indoor surfaces;
- Agricultural spraying of "grey" water.

Each of these processes leads to generation of aerosol droplets of different characteristics in terms of their size and initial speed. These two factors are of critical importance for the fate of the aerosols in the air, and in a probabilistic sense determine the distance travelled by the droplets, change in size during transport as a function of ambient temperature and relative humidity, their survival, and the location of deposition on indoor surfaces. Two of these processes, including humans as a source of droplets and sewage atomisation are briefly discussed below.

Humans as a source of droplets

Expiratory human activities such as breathing, coughing, sneezing or laughing result in droplet generation by the wind shear forces. Droplet atomisation from the respiratory tract arises from the passage of an air-stream at a sufficiently high speed over the surface of a liquid; toques of liquid are drawn out from the surface, pulled thin and broken into columns of droplets (Hickey 1996). Each of these processes leads to droplets of different size and originating from different areas of the upper respiratory tract. The differences in size result from variation in air pressure and speed in different parts of the respiratory tract, in much the same way as explained above for the atomization process. The significance of each of these activities in the spread of infection depends on a number of factors, including: (1) the number of droplets it produces, (2) their size, (3) content of infectious agents and, (4) the frequency of its performance. For example, sneezing and coughing produce many droplets, while speaking laughing and breathing produce few. The latter activities, however, are more frequent.

The content of infectious agent expelled by an infected person depends, among other factors, on the location within the respiratory track from where the droplets originate. The reason for this is that the pathogenic organisms tend to be confined to certain localities, especially to the tonsil and to the larynx and seldom at the front of the mouth. Thus to assess the potential for infection via airborne droplet route, it is important to develop an understanding about the localities from which droplets originate during various expiratory activities, and the numbers of droplets arising from each site. The likely sites of droplet origin are suggested by consideration of the mechanism of atomisation and the mechanism of each of the respiratory activities. In particular air velocities high enough for atomization are produced when air is forced out through some parts of the respiratory tract which have been greatly narrowed. The front of the mouth is the site of narrowing and the most important site for atomization, as this is almost closed by approximation of the tongue, teeth and lips. Narrowing of passages, and thus increased likelihood for atomisation also occurs at the throat (nearly closed by approximation of the tongue, tonsils and soft palate), the glottis (nearly closed by the vocal folds), in bronchi (obstructed by secretion), in the nasal cavity (obstructed by secretion), and the anterior nares (the narrower parts of the normal nasal passage). Therefore, since most droplets originate at the front of the mouth, which is the location where normal commensal organisms are present in healthy people (or artificially introduced organisms for the purpose of infection studies), but not the pathogenic organisms, aerial infection is much more limited than would be suggested by the pure physical studies of droplet generation. Also pathogenic organisms carried in the respiratory tract are not expelled as readily, nor in as great numbers, as could be implied just from the mechanisms of droplet generation.

Early investigators (from the 1920s to 1940s) believed that the vast majority of droplets generated through expiratory human activities are in the supermicrometer size eg: (Wells 1934), (Duguid 1945) and (Jennison 1942). This was because the techniques they had available at the time to conduct such studies were insensitive to smaller droplets. The techniques available then were based on counting of large respiratory droplets after collection on a slide or on a culture plate, exposed directly in front of the mouth. The stain marks left on the slide after evaporation of the droplets were counted under the microscope, or the colonies of commensal mouth organisms or *B. prodigiosus* (if the mouth has been artificially infected) were counted by examination of the culture plate after incubation. This method is adequate for counting larger droplets (> 10 - 20 μm) with large inertia that deposit on the plate. Smaller droplets, which have little inertia (and which also evaporate fast, as described above), are underestimated by these methods as they follow the air stream and are not deposited. Other methods available at the time for larger droplets (> 5 – 10μm) were by counting droplet images on enlarged, high speed, dark field photographs (Jennison 1942), and for smaller droplets (down to about 1 – 2μm), sampling with a slit sampler after the droplet spray was evenly distributed in the air. Improvement of the methods relied upon artificial staining of the droplets to improve its efficiency.

Table 1 presents a compilation of the results from the work of (Duguid 1945), who employed several techniques available at the time to study the number of droplets generated during human expiratory activities, and the region of droplet origin. Overall, the authors conducted hundreds of different tests enabling estimation of droplets in the size range from 1 – 100 μm. In general, 95% particles were smaller then 100 μm, and the majority were in the range from 4 - 8 μm. It can be seen that nearly all of the small droplets originate from the front of the mouth; only relatively few, if any, from the nose or from the throat.

More recent studies, involving optical particle detection techniques capable of measurements down to fractions of a micrometer, suggested that in fact the majority of these particles are in the submicrometer size range (Papineni and Rosenthal 1997). In summary, the study conducted by (Papineni and Rosenthal 1997) involved five healthy individuals and employed optical particle counters with a particle detection range from 0.3 μm and also electron microscopy as droplet detection methods. Contrary to the earlier studies, this study showed that 80 – 90% of particles from human expiratory activities are smaller than 1μm. The study also showed that the highest droplet concentrations were commonly generated during coughing and the lowest from nasal breathing; however, there was large inter-subject variability in concentrations emitted during various activities. For example, it was shown that coughing in general results (as expected) in many more particles being expelled than mouth breathing; however, for one subject, mouth breathing actually produced a higher concentration of droplets larger than 1μm compared with coughing. The results of the study suggest that exhaled breath may be considerably more effective in the transport of viruses (size of the order of 0.1μm) as compared with bacteria (> 1μm); nevertheless, transport of bacteria is also possible. One important issue, which was not addressed by the study, was the relationship between the original droplet size and the size measured. Before detection in the instrument, the droplets spent considerable amount of time in the air, which, as presented below, could have been sufficient for drying of medium size droplets to the droplet residue. Therefore, the measured droplets could in fact have been the dry droplet residue. It should also be pointed out that only healthy individuals were studied by (Papineni and Rosenthal 1997), while (Duguid 1945) investigated people with chest infection. The mechanisms of droplet generation by the healthy and the sick are expected to be different, which could be another factor contributing to the differences between the two studies.

Table 1: *The number of droplets generated during human expiratory activities and the region of their origin as compiled from (Duguid 1945).*

Activity	**Number of droplets generated (range)**	**Region from where they came**	**Presence of droplet 1-2 μm (droplet residue)**
Normal breathing (for 5 minutes)	0- few	nose	Some in this range
Single strong nasal expiration	Few – few hundred		Some in this range
Laughin (for 1 min)	0- few	Faucial region	
Counting softly (1 – 100)	Few – few dozen		
Counting loudly	Few dozen – few hundred	Front of the mouth	Most in this range
A single cough (mouth open)	0- few hundred	Faucial region	Some in this range
A single cough (mouth initially closed)	Few hundred- many thousand	Front of the mouth	Most in this range
Single sneeze	Few hundred thousand – few million Few- few thousand	Front of the mouth Both from the nose and the faucial region	Most in this range Some in this range

One other process of virus atomisation through human expiratory activities, which is somewhat different to the processes discussed, is vomiting. It has been shown that infected individuals can shed up to 10^7 virus particles per ml of vomit (Barker, Stevens et al. 2001). Atomised droplets of various sizes become airborne with the potential for direct infection by inhalation or through the contact of re-entrained dust containing the virus. Spread of viral infections through atomised vomit is a significant route of infection in diseases which cause frequent vomiting, such as NLVs. For example, during a school outbreak of Norwalk-like virus, students were significantly more likely to become sick after a student vomited in the classroom (Marks, Vipond et al. 2003). It could also be significant for other types of viral infections. For example, vomiting by a SARS infected person on the corridor of Metropol Hotel in Hong Kong in 2003 is believed to have caused a series of infections. It is not, however, clear what the pathway of infection was: primary airborne droplets, droplet residue, or re-entrained infected dust.

In summary, from the studies reported so far, there is some understanding of the size of droplets generated directly by humans through the fact of their existence, during various human expiratory activities, and the region in the respiratory tract where they originate from. However, since there have been only a handful of studies conducted with the application of modern techniques capable of detecting submicrometer particles, it is important that more work is done in this area to develop a better understanding of the mechanism of droplet generation. There is also some understanding of the content of infectious agents in the droplets from experiments on healthy individuals artificially "marked" with the agents. However, there is much less knowledge of the content of real infecting agents expelled by infected individuals, which is of key importance in understanding the actual spread of viral infections. It is also important to better understand the degree of interpersonal variability in the process of droplet generation, as this knowledge could be critical in explaining the "super spreading" capabilities of some individuals.

A limiting factor in the studies on infectious droplet generation by infected people is the complexity of experimental techniques for detection of viral content in airborne samples. Currently the measurements on spatial distribution of viral content of aerosol particles involve sampling of air from selected locations through a liquid impinger for detection and quantification of the viruses, using RTD-PCR technique. Numerous studies have been performed that utilise PCR techniques to detect viruses. However, variations of this technique have been necessary to achieve specific aims of individual research projects. More recently, PCR has been utilised to quantise viral content. A real-time RT-PCR assay of SARS-coronavirus allowed viral loads of clinical specimens to be quantified (Poon, Chan et al. 2003). Consequently, it was demonstrated that early diagnosis of the SARS virus could be achieved. Real-time PCR can produce and quantise amplicons using intercalating dyes or fluorescent probes or primers (Richards, Watson et al. 2004), (Stram, Kuznetzova et al. 2004), 2004). These, and other similar studies, have shown that the development of PCR methods has created a highly sensitive technique to detect and quantise viruses. However, research into the use of RR-PCR has also highlighted the fact that its application to detection of viruses in aerosols is very experimental, and that a number of aspects need to be developed before it may be successfully applied. *In general, one of the main limitations is that preventively large amounts of air need to be sampled to allow quantification. Therefore, studies on the viral content of droplets generated from infected human expiratory activities and their fate in the air after expiration are still very complex and experimental.*

Spread of viruses from faeces

It has been showed that infected individuals can shed up to 10^{12} virus particles per g of faeces (Barker, Stevens et al. 2001). The main mechanisms for atomisation of faeces are sewage aerosolation from toilets during flushing, and also during its transport in building downpipe systems. In general, not much quantitative research has been done into the mechanism of sewage atomisation through the above processes in terms of the size of droplets generated, and thus their fate in the air and the potential for virus spread.

Atomisation of sewage from toilets is likely to have a larger potential for disease spread, as it occurs during each use of the toilet. Atomised droplets could be directly inhaled, or deposited on the surfaces in a bathroom, leading to contamination of hands (Rusin, Orosz-Coughlin et al. 1998). More research has been done on the presence of bacteria from atomised toilet sewage than viruses, showing different levels of contamination in different studies. For example, cultures were made of air, water and surface samples taken from hospital toilets (Newsom 1972) demonstrating that the level of contamination was much less than expected. In another study, microbial aerosols were monitored after toilet flushing. A toilet was contaminated with *Escherichia coli* and agar plates were exposed throughout the room. Flushing the toilet caused bacteria to be detected in the area immediately surrounding the toilet within the first two hours and after up to six hours in a more random distribution of *E. coli* in the room. Bacteria were also found to have settled on the toilet (Gerba, Wallis et al. 1975).

The latter process, in which a virus is spread by contaminated droplets atomised in the building downpipe system, should in principle be prevented if the sewage removal system operates properly without leaks or the possibility for sucking any droplets outside the system. As it has been demonstrated, however, this is the process that most likely led to SARS virus spread and subsequent infection in the Amoy Garden in Hong Kong (as described below).

DROPLET FATE IN THE AIR

Following formation or introduction into the air, airborne particles undergo a range of physical and chemical processes that change their chemical composition, physical characteristics and concentration in the air. The type of physico-chemical processes that could be of importance in affecting fate of airborne droplets include: evaporation, interaction with other types of particles, transport and removal from the air by deposition on surfaces. Particles in the air are subjected to Brownian motion, gravity, electrical forces, thermal gradients, electromagnetic radiation, turbulent

diffusion, inertial forces and relative humidity (Baron and Willeke 2001). Diffusion is an important mechanism of transport for particles in the lower submicrometer range, leading to coagulation with, or attachment to, other aerosol particles. For particles larger than 1 μm, gravity is more significant than Brownian motion (Cox 1995.) However, the effect of gravity on a particle is countered by the drag or frictional force exerted on that particle. As an example, Table 2 presents a relationship between droplet size and falling time calculated from Stokes' and Newton's laws. The calculations were based on the assumption that the droplets are introduced into the air without an initial speed. The assumption is not true, as the speed depends on the generation process. For example, in relation to human expiratory activities this speed is high for coughing and lower for breathing.

Table 2*: Droplet falling time as a function of size(compiled from (Wells 1934)*

Droplet dimeter [μm]	Falling time of 1 m [s]
1000	0.3
100	3
10	300
1	30,000

Figure 1 presents changes to pure water droplet diameter as a result of evaporation calculated for the purpose of this discussion for three different initial droplet sizes (1, 10 and 100 μm) and for different conditions of relative humidity (RH). It can be seen that droplets with sizes of the order of 1 μm evaporate within a few milliseconds, even under the conditions of high relative humidity. Droplets of the order of 10 μm exist for up to a few tens of a second; while very large droplets, 100 μm in diameter, survive for up to almost a minute.

It can be seen from Table 2 and Figure 1 that smaller droplets settle very slowly and therefore evaporate before settling, while larger droplets settle rapidly and do not evaporate much during this time. *In general, under standard atmospheric conditions, droplets smaller then 100 μm will evaporate before reaching the ground. But the evaporated droplet residue would remain resuspended in the air for prolonged periods of time.* Formation of droplet residue, their size and composition depend on the composition of the original droplets. This is illustrated in Figure 1, which presents the change in size of droplets of saline solution of 0.86% (NaCl – similar to the solution in human saliva). It can be seen that initially the change in droplet size as a result of evaporation is similar to the change of pure water droplets; yet, while pure droplets evaporate completely, the saline droplet evaporates to form a solid droplet residue. This process is very fast and reduces saline droplets to salt residue.

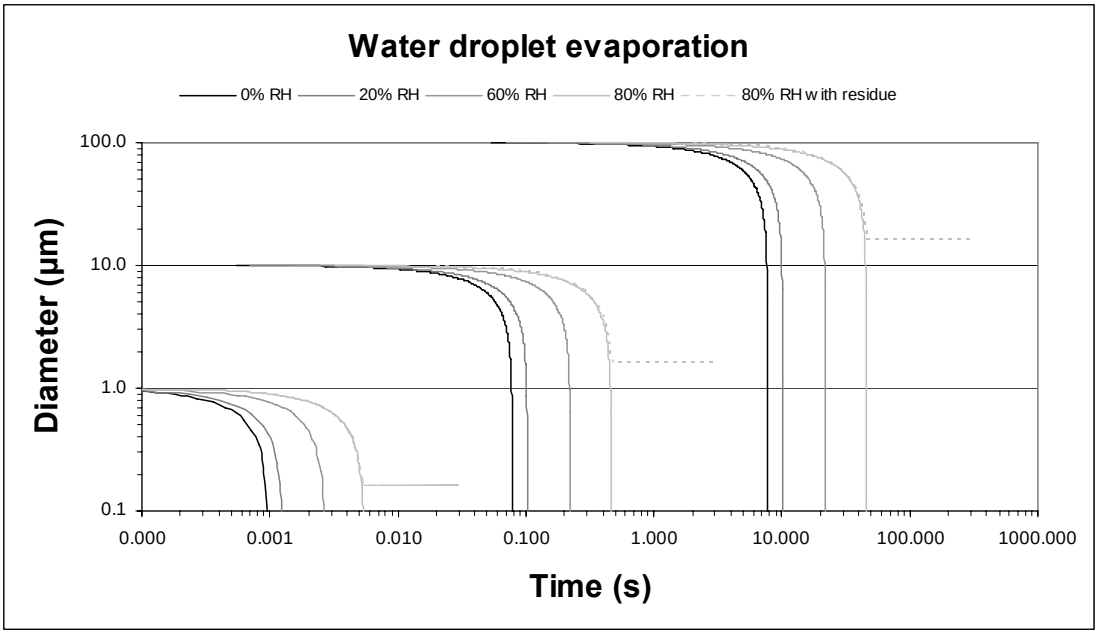

Figure 1: *Changes to pure water droplet diameter as a result of evaporation calculated for three different initial droplet sizes (1, 10 and 100) µm and for different conditions of relative humidity (RH). Broken curves present the size of dry droplet nuclei for droplets, which were 0.86% NaCl solutions.*

The droplets produced from body secretion such as sneezing and coughing are not constituted of pure water and have a significant amount of residue (dissolved substances). Hence relations deduced for pure water droplets cannot be directly applied. However, droplet size is still the main parameter in the process. The final size of the droplet once it has evaporated to its crystallisation diameter (the minimum diameter of the dry residue from the droplets), will depend, as it has been shown in Figure 1, on the amount of the material dissolved. If the droplets contain infectious bioaerosols, such as viruses, they too would remain in the air after the liquid content evaporated.

Transmission of infection from an infected person to a new host depends on a number of factors related to particle dynamics, as discussed above. For example, a study of ferrets found that transmission of influenza from ill to susceptible ferrets occurred despite the ferrets being separated by a long, straight air duct or by 's' or 'u' shaped ducts (Andrewes and Glover 1941). It was considered that large respiratory droplets could not move around the bends of the ducts whereas the smaller droplet residue could. A mouse model study also supported the transmission of influenza via droplet residue (Schulman and Kilbourne 1962).

The understanding of size distribution of droplets and droplet residue related to various release mechanisms and their subsequent transport is still limited, and perception of the droplet dynamics, not free of misconceptions. In particular, it has been believed that droplets larger than 20µm rapidly settle onto surfaces (Gold and Nankervis 1989), while droplets between 0.5 and 20µm remain in the air for long periods and are more likely to be captured in the respiratory tract and produce infection (McCluskey, Sandin et al. 1996). *From the above discussion it can be concluded that droplets do not remain in the air for any considerable periods of time as they evaporate very quickly. However, both these size ranges result in solid airborne residue and can be suspended in the air for prolonged periods of time.* Another misconception commonly encountered in the literature (the background of which has not, however, been discussed in this paper) is that droplets smaller than about 0.5µm tend to remain in the respiratory air flow and are not retained in the alveoli (for example (Gold and Nankervis 1989). *However, it has been shown that of the order of 50% particles in the lower submicrometer range deposit in the the respiratory tract* (Morawska, Barron et al. 1999).

When considering the behaviour and ultimately the fate of biological particles in the air it is important to keep in mind that the concentration of these particles is usually significantly lower than the concentration of particles that are not of biological origin. This implies that the behaviour of biological particles in the air cannot be investigated in isolation; but consideration should be given to the characteristics of non-biological particles (concentration, size distribution), as the presence of the latter could have an important impact on biological particles. In general, the nature of the association between a virus and its carrier particles has not been well established, as demonstrated in a recent study on foot-and-mouth disease (Gloster and Alexandersen 2004).

Other important factors that need to be considered in transmission of infection are infective dose and virulence. During transport, the concentration of airborne infectious agents decreases through mixing and dilution; however it should be kept in mind that sometimes it is a single organism that can cause infection. For example, the infective dose for NLVs may be as low as 10 – 100 particles (Caul 1994); while for the rotavirus, 10 particles (Ward, Bernstein et al. 1986).

Role of relative humidity in survival of the viruses

Survival capability in the air is another key factor in virus spread, where in addition to the characteristics of the droplets upon release, also the physical characteristics of the environment play an important role. In particular, ambient temperature and relative humidity are critical parameters for bioaerosol survival capability. For example, as droplets evaporate they become smaller, providing less protection to the virus to remain undamaged.

There have been a number of studies conducted to investigate survival of airborne viruses under different ambient moisture and temperature conditions. For example, several studies including (Ijaz, Sattar et al. 1985) on the airborne human coronavirus 229E or (Karim, Ijaz et al. 1985) on Rhinovirus-14 showed that low temperature improved the survival ability of the viruses at a high relative humidity. The airborne human coronavirus 229E (HCV/229E) was studied under two different temperatures and low, medium or high relative humidity (Ijaz, Brunner, Sattar, Nair and Johnson-Lussenburg, 1985). It was found that high relative humidity is deleterious to the survival of aerosolised HCV/229E. However, low temperature improved the survival ability of the virus at a high relative humidity. It was proposed that, “under conditions of high humidity, the fluidity of the lipid-containing envelope is stabilised at low temperature, thus protecting the virion” (Ijaz, Sattar et al. 1985). Rhinovirus-14 survives better in high humidity when it is at a low temperature (Karim, Ijaz et al. 1985). This is also the case for rotavirus SA11 (Sattar, Ijaz, Johnson-Lussenburg and Springthorpe, 1984). At low and medium RH the infectivity of the airborne virus was rapidly lost. At 24°C the survival of Japanese B encephalitis virus as an aerosol is inversely related to relative humidity (Larson, Dominik et al. 1980).

From the above and other published studies it can be concluded that in general, viruses with lower lipid content have greater stability at high relative humidity than lipid containing viruses (Pillai and Ricke 2002). Viruses that possess a lipid envelope are more stable in dry air; whereas viruses without a protective envelope are more stable in moist air (Roe 1992). Viruses that are protected by a lipid envelope include influenza, parainfluenza, respiratory syncytial and corona viruses, and thus they are expected to be more stable under drier conditions; whilst viruses without protective envelopes such as rhino, entero or adeno viruses, are more stable under humid conditions. Another general conclusion is that viruses are more stable at low ambient air temperatures. *Hence virus particles present in aerosol remain infective for longer periods of time during cold weather than during warmer weather. For example, influenza epidemics usually occur during the cold winter season when low humidity is more prevalent. However, conditions like this are also created in modern air conditioned buildings: cold and dry.*

Deposition on surfaces

Bioaerosols can be deposited on surfaces either by gravitational sedimentation of the original droplet in which they are contained, or by diffusional deposition of the droplet residue. The former occurs in the immediate proximity of the sources (e.g. humans generating the secretion), the latter, however, can occur at considerable distances from the sources, as the submicrometer droplet residue can remain suspended in the air for extended periods of time and travel considerable distances. Survival potential on a surface depends on the nature of the surface, particularly its moisture content, and also on the type of the virus and its tolerance of dry conditions. For example, the influenza virus has been found to survive in dust for a number of days depending upon the surface on which it was deposited (Derrick 1941). The virus can then be spread either by direct contact (for example touching of the surface by hands) or by aerial transfer of dried virus on dust particles.

Modelling of droplet transport

Modelling of droplet transport based on the theory of aerosol transport processes using quantitative equations was presented by (Hinds 1999). Previous models based on the Gaussian plume model (Turner and Sassman 1996), which were developed for spray irrigation processes, cannot be used in this case for several reasons. These models were developed for larger distances and for significantly larger transport times. In the case of indoor environments, the linear dimensions over which the modelling will be developed are significantly smaller. Also the size of the droplets is different than those generated in irrigation processes. It has been also stressed that such predictive models do not take into account particle size, a key factor in aerosol transport.

EVIDENCE OF AIRBORNE ROUTE AS A MECHANISM FOR INFECTION SPREAD

There is an ample amount of evidence or indications that airborne route of infection occurs. This evidence comes from studies showing that:

1. *Spread of infection occurred despite unlikelihood of any direct contact (cohabitation of the same indoor microenvironment), or indirect contact (touching of the objects infected by the index case).*

   An example of this is SARS spread in Amoy Gardens housing estate in Hong Kong, where the infection of over 300 people from over 150 apartments in 15 blocks covering thousands of square meters and rising over 100 m above ground was linked to one index case visiting one of the apartments. Retrospective research suggested that atomised sewage containing faeces from the infected person in Block E of the estate was sucked from the downpipe through a dry floor waste and ejected from the building through a bathroom exhaust fan. Virus-laden particles then entered the re-entrant and upper story faults through open windows (Yu, Li et al. 2004). Using multi zone simulation (Li, Duan et al. 2005) subsequently explained the spread of virus between flats of Block E, with the predicted hourly average of virus-laden bioaerosol concentrations matching the spatial infection pattern. Residents of the floors at the middle and upper levels in Building E were at significantly higher risk than the residents on the lower floors. This is consistent with the rising plume of contaminated warm air in the air shaft generated from a middle level apartment unit. The distribution of risk in buildings B, C, and D corresponded well with the three dimensional spread of virus-laden aerosols predicted with the use of CFD modelling (Yu, Li et al. 2004). The study stressed the dual role played by natural ventilation in high rise buildings: a positive role in diluting the concentration of bioaerosols and a negative role by carrying them between flats. While airborne transmission route in the Amoy Gradens estate is now a commonly accepted explanation, at the time of the infection and after it occurred, many hypotheses were proposed including the possibility of an animal vector, namely contaminated rats (Ng 2003).

2. *There is a correlation between building factors related to air circulation and the rate of occurrence of infection.*

   It has been shown in studies conducted in army barracks, jails, hospitals and office buildings that among the most important related building factors are rate of ventilation and rate of air recirculation, with low ventilation and recirculation of air increasing the potential for virus

spread(Mendell, Fisk et al. 2002). It has been also shown that there is a correlation between disinfection of recirculated air and infection occurrence. Another building factor included in this class is occupation density, with increased overcrowding often correlating with increased rates of infection. The importance of increasing distance between people has been particularly recommended in hospital settings, with two "arm lengths" being a minimum, as some physicians believe. In the cases of overcrowding, however, it is not only air transport that could play a role in infection spread but also direct contact and transmission through infected surfaces.

Overall, 6 of 11 studies reviewed by (Mendell, Fisk et al. 2002) showed that some particular characteristics of buildings or indoor environments were associated with changes in infection rates of the order of up to 50%. However, there are studies that did not find the impact of indoor characteristics on infection rate. For example, studies on aircraft cabin air recirculation and symptoms of cold conducted among 1100 passengers travelling from the San Francisco area to Denver, Colorado, found no evidence that aircraft cabin recirculation increases the risk for upper respiratory tract infection symptoms in passengers travelling aboard commercial jets (Zitter, Mazonson et al. 2002).

3. *There is spatial distribution of cases correlated with the flow direction from the infection sources.*

Examples of this include SARS spread in a hospital ward in Hong Kong (Li, Huang et al. 2005) or spread of TB from an infected person during an airplane flight(Kenyon, Valway et al. 1996). Using retrospective, on-site measurements of the ventilation design and air distribution, and computational fluid dynamic (CFD) simulation showed that there was an association between the concentration decay from the index patient's bed and the spatial infection pattern in Ward 8A of the Prince of Wales Hospital in Hong Kong in March 2003 (Li, Huang et al. 2005). If in the above cases the spread was through contaminated surfaces and hands, it would be expected that the spread of infection would be random.

It should be stressed that the evidence of an airborne route of infection obtained through all of the above types of cases, while convincing, is only indirect. The evidence is most compelling in case type 1, for example in the Amoy Gardens estate there was only one infected person, and no other sources of infection identified. The situation is not as clear in cases under type 2 and 3. No reported associations confirm causal relationship between aspects of indoor work environments and communicable respiratory infections.

One conclusion that could be derived from the above discussion is that setting the most important building parameters, such as ventilation, recirculation, filtration and occupancy, according to the current understanding of their optimal ranges would result in a lowering of the potential for infection spread. This is certainly true, but whether this is the limit of what can practically be achieved in the minimisation of infection spread is not known. Studies on the effect of the improvement of building parameters should be conducted with a simultaneous focus on the impact of this on virus spread and optimisation of the system.

It should also be stressed that when considering optimisation of temperature and humidity for an indoor environment it should be kept in mind that increasing or decreasing these two parameters will decrease survival of some of the infectious aerosols, but will help others to survive (as explained above).

A BROADER PICTURE: RELATIVE IMPORTANCE OF DIFFERENT ROUTES OF INFECTION SPREAD

It has been well established that a number of routes of infection spread exist and they all have been shown to play a significant role in certain situations or under specific types of conditions. A key question, however, is what is the relative importance of individual routes in different environments and for different infectious agents?

In the previous sections, airborne spread of infection was discussed, with the provision of compelling evidence for the significance of this route. However, there is substantial evidence on the significance of person to person transmission via the hands and contaminated fomites in the spread of viral infections. Handling fomites such as eating utensils, towels, or doorknobs, inadvertently contaminated with fresh secretion or vomit from an infected person and then transferring the virus from the hands to the eyes, nose or mouths are further routes of spread. For example (Bellamy, Laban et al. 1998) showed that in domestic environments, amylase (an indicator of saliva, sweat and urine) was found on 29% of surfaces that were frequently handled or in contact with urine. (Rheinbahen, Schunemann et al. 2000) showed that at least 14 persons can be contaminated one after another by touching a contaminated door handle.

A significant challenge in assessing whether contamination found on hands or other surfaces might represent a hazard is that the infectious dose can vary significantly according to the pathogenicity of the organism and the immune status of the host. Review of the current understanding of infection spread in homes and community settings led (Barker, Stevens et al. 2001) to conclude that adequate understanding of the potential of surfaces to act as unidentified vectors of pathogens in the transmission cycle is still lacking and is very much needed.

Another aspect investigated by (Barker, Stevens et al. 2001) in his review of 15 studies reported on this topic was the effect of hygiene measures in the control of infection. The intervention measures taken in these studies mainly included education on hand washing, reinforcing of hand washing and, in a few of the studies, also cleaning of surfaces. All of the studies showed reduced or significantly reduced infection rates. For example, a 50% reduction in illness was observed in a hand washing group compared to a non-hand washing group in a children's daycare centre (Black, Dykes et al. 1981). Hand washing would appear to be the cheapest measure for prevention of infection spread; yet it is very difficult to enforce as found by many investigators, and not only among general community but also among health practitioners. For example in a surgery department in the UK, clinicians washed their hands between examinations in only 41% of cases (Daniels and Rees 1999).

The route of spread has been shown to also depend on the virus itself. It was found for example that Respiratory Syncytial Virus (RSV) spreads predominantly via direct and indirect contact rather than by droplets or droplet nuclei (Hall and Douglas 1981), even though it is a respiratory virus. Studies of nosocomial RSV infection conducted at a children's hospital also supported the importance of indirect contact spread in the transmission of this virus (Leclair, Freeman et al. 1987). Some diseases, however, such as influenza, have been more commonly linked to airborne spread (Goldmann 2000). Studies of the rhinovirus showed that its spread could be linked to both these routes. For example, (Gwaltney Jr and Hendley 1982) emphasised the importance of indirect contact spread of rhinovirus via contaminated fingers and fomites, with little evidence suggesting transmission via droplets or droplet nuclei. However, other studies of rhinovirus strongly support transmission via the air and not via direct contact (1987) (Myatt, Johnston et al. 2003).

In summary, it has been concluded that improved standards of education, personal hygiene (particularly handwashing) and targeted environmental hygiene may have a considerable impact in the control and prevention of infectious organisms. However, the existing evidence for cross-contamination as a causative factor in outbreaks, has always been circumstantial and there is a pressing need for quantitative epidemiological data on the assessment of the impact of hygiene in infection spread.

ECONOMICS OF INFECTION SPREAD

While everybody, whether a lay person or an expert, would agree that infection spread is undesirable to the individual and to communities, the costs of the spread or economical benefits of prevention are rarely quantified. Viral infections remain a major global cause of morbidity and mortality, with the majority of morbidity cases not reported, yet causing loses. Morbidity leads to large economic and social impacts through absenteeism, lost productivity and costs of medical

treatment. For example, UK estimates show that adults suffer as many as 2 to 5 colds per year and infants and preschool children have about 4-8 colds per year (Sperber 1994).

Another analysis showed (Wheeler, Sethi et al. 1999) that as many as 1 in 5 people in the general UK population develop infectious intestinal disease each year, with an estimated 9.4 million occurring annually. However this figure might be much greater, as the majority of cases are unreported. As an example, the same study reported that for every case of rotavirus and NLV reported to national surveillance, a further 35 rotavirus and 1562 cases of NLV occur in the community. Surveillance data from the UK show that reported outbreaks of viral intestinal infections have increased rapidly over the last decade or so. In another part of the globe, in Australia, there are over 60 thousand hospital separations recorded each year by the National Notifiable Diseases Surveillance System, with the principal diagnosis of influenza or pneumonia, which represents over 1% of all hospital separations. In 1996 alone, influenza and resulting conditions such as pneumonia claimed the lives of over 1600 Australians aged 65 and over. Disease notifications and hospital admissions do not capture common infections such as colds or the respiratory syncytial virus, nor the impact of the viral diseases on human health.
In the United States there have been estimates conducted of the total communicable respiratory infectious occurring annually as well as the degree of its potential reduction (Mendell, Fisk et al. 2002). It has been estimated, for example, that building influenced communicable respiratory infections (influenza, cold, TB) amount to: $10 billion in health care costs, $19 billion in costs arising from absence due to illness, and $3 billion in other performance losses. It was also assessed that there are 52 million cases of influenza and common cold a year of which 10-14% (5 -7 million cases) could be prevented, resulting in a saving of $3 to 4 billion.

Therefore the benefits of infection prevention could be huge. Major outbreaks of communicable diseases are able, as the recent SARS outbreak has shown, to paralyse economies and businesses on a vast scale. Yet, as it has been concluded “The potential health and economic benefits of improving indoor work environments are largely unrecognized in the USA”. (Mendell, Fisk et al. 2002). This statement is very true in relation to the rest of the world as well.

Recently in the United States, the National Occupational Research Agenda (NORA) of the National Institute for Occupational Safety and Health (NIOSH) identified building-influenced communicable respiratory infections as one of the priority research topics in the area of indoor non industrial environments. It has been demonstrated that many current building codes, standards and guidelines, although intending to be health proactive are based primarily on practical experience within the building sector, or on non-health related criteria such as perceived acceptability of air, and therefore they are not sufficiently health protective.

SUMMARY

Human environments, including homes, offices, schools and other settings, always contain potentially harmful microorganisms. In considering measures against infection spread, the target is not eradication of these microorganisms, but limiting the risks of exposure to prevent larger disease outbreaks. If only a fraction of common cold cases or hospital separations with a principal diagnosis of influenza or pneumonia could be prevented by virtue of improved methods for limiting the spread, millions of people world wide would remain healthy and billions of dollars could be saved every year. It has been shown in this paper that in order to take informed measures against infection spread, there is a pressing need to develop a better understanding of the science of infection spread. There are many reasons why progress in this area has been relatively limited, including:

- significant experimental complexity of simultaneous characterisation of the microbiological and physical nature of virus-containing particles, and the need for an interdisciplinary approach.
- lack of scientific methods and techniques for accurate quantification of virus particles in the air. It is only recently that advanced techniques such as PCR became available, which, with appropriate research expertise, can be used in a quantitative way in application to the types of

viruses selected for investigations.

- lack of realization of the importance of the dynamics of virus spread. Reviewing literature on bioaerosol dynamics, it can be seen that some major international events tended to create interest in this area and the realisation of its importance (such as during World War II and other periods when biological warfare was of international interest, and at times of influenza or other respiratory pandemics), which was manifested in an increase number of publications around those times, after which the interest declined until the next major event.

The existing limitations in scientific knowledge of infection spread include the understanding of:

1. The size distribution of droplets related to various release mechanisms
2. The relationship between the initial size of the droplets and their change in size due to evaporation under different environmental conditions to enable quantitative assessment of the effect of this process on virus stability.
3. The mechanisms responsible for transport and spread of the agents in common types of indoor environments, which would enable meaningful simulation of virus transport in indoor environments to predict the likely pathways of human infections.

To address the above and related questions there is a need for faster, easier and cheaper detection methods, ideally real time methods. Since the role of the environment in the survival of airborne microorganisms is extremely complex, for practical application to the control of airborne infectious agents, research must move from the laboratory test chambers to the actual indoor environments, with previously developed standardized techniques and approaches (Cole and Cook 1998).

Better understanding of this area of science would enable development of more targeted strategies for engineering controls for the prevention of airborne infectious disease transmission and for developing day to day solutions for typical infectious aerosols, particularly in situations of serious disease spread.

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