Dynamics of infectious disease transmission by inhalable respiratory droplets

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Transmission of respiratory infectious diseases in humans, for instance influenza, occurs by several modes. Respiratory droplets provide a vector of transmission of an infectious pathogen that may contribute to different transmission modes. An epidemiological model incorporating the dynamics of inhalable respiratory droplets is developed to assess their relevance in the infectious process. Inhalable respiratory droplets are divided into respirable droplets, with droplet diameter less than 10 μm, and inspirable droplets, with diameter in the range 10–100 μm: both droplet classes may be inhaled or settle. Droplet dynamics is determined by their physical properties (size), whereas population dynamics is determined by, among other parameters, the pathogen infectivity and the host contact rates. Three model influenza epidemic scenarios, mediated by different airborne or settled droplet classes, are analysed. The scenarios are distinguished by the characteristic times associated with breathing at contact and with hand-to-face contact. The scenarios suggest that airborne transmission, mediated by respirable droplets, provides the dominant transmission mode in middle and long-term epidemics, whereas inspirable droplets, be they airborne or settled, characterize short-term epidemics with high attack rates. The model neglects close-contact transmission by droplet sprays (direct projection onto facial mucous membranes), retaining close-contact transmission by inspirable droplets.

Keywords: respiratory droplets; aerosol; influenza; dynamics; epidemic

1. INTRODUCTION

An essential element in understanding the epidemiology of infectious diseases is their mode of transmission. For some infectious diseases, the routes of transmission are multiple and their relative importance and dynamics are neither well described nor well understood. The identification of the dominant transmission mode is important because efficient and effective control strategies depend on it.

For respiratory infectious diseases, influenza probably being the most prominent example, three different, mutually non-exclusive, main modes of respiratory pathogen transmission have been identified (Tellier 2006; Brankston et al. 2007). The classification used in the medical literature considers ‘contact’, ‘droplet’ and ‘airborne’ transmission. Contact transmission (be it direct or indirect) arises from contact with pathogen-containing droplets: direct contact transmission refers to physical contact and transfer of pathogens from an infected person to a susceptible, whereas indirect contact transmission refers to contact with fomites and subsequent transport of the pathogen via, for example, hands to the upper region of the respiratory tract (mouth, nose). Droplet transmission occurs via large droplets that are generated by a close expiratory event (coughing, sneezing): they deposit immediately onto a susceptible’s mucous membranes. As large droplets gravitationally settle quickly droplet transmission constitutes a transmission mode only for close contact. Airborne transmission (also referred to as aerosol transmission) occurs via inhalation of small respiratory droplets (also referred to as ‘droplet nuclei’) that are small enough to remain airborne.

Not all modes of transmission are relevant for all respiratory infectious diseases; each transmission mode may affect different locations in the respiratory tract since deposition in the respiratory tract depends on droplet size. For example, the airborne mode is the most relevant for tuberculosis since the reception site is the lower respiratory tract, whereas influenza reception sites may be anywhere in the respiratory tract rendering all three modes relevant.

Respiratory droplets, all droplets generated by an expiratory event—coughing, sneezing, laughing, talking, breathing—have diameters d that cover a large
size range from approximately 0.6 to more than 1000 \mu m. Droplets responsible for transmission by inhalation have also been classified as respirable and inspirable (Nicas & Sun 2006). Respirable droplets remain airborne sufficiently long to provide a mechanism for airborne transmission. Inspirable droplets are larger: they are either inhaled at close contact or they gravitationally settle very fast. They contribute to infection transmission by inhalation as they may be inhaled immediately after generation (e.g. during the first breath) instead of direct deposition onto the upper respiratory tract. We shall refer to these two droplet classes as ‘inhalable’ droplets. Nicas & Sun (2006) consider ‘respiratory droplet spray’ an alternative description to droplet transmission. Furthermore, they argue that respirable droplets have an aerodynamic diameter (after evaporation) \( d < 10 \mu m \), whereas the size of inspirable droplets is in the range \([10, 100] \mu m\).

2.2. Model description

Emitted respiratory droplets are of varying sizes characterized by their number distribution, namely the epidemic by determining the dominant transmission mode, and the duration and incidence of the epidemic. Results suggest that the duration of an epidemic is inversely related to the pathogen load of the droplets constituting the dominant transmission mode. We note that the model is general enough to be applicable to the transmission of any respiratory infection whose infectious agent is transported by inhalable respiratory droplets.
number of droplets per unit air volume as a function of diameter. Size, specifically diameter, is the most important physical property of a droplet. The droplet diameter determines whether a droplet will settle under gravity (it determines its airborne residence time, and hence whether it is likely to be inhaled) or whether it will evaporate before settling (evaporation depends, in addition, on the chemical composition of the droplet), thereby converting a large to a smaller droplet. Hence, the characteristic diameter of a droplet relevant to transmission via inhalable droplets is determined from its settling and evaporation times. We neglect hygroscopic growth in the respiratory tract, a process inverse to ambient-air evaporation.

2.2.1. Monodisperse droplet number distribution. Consider a closed population of \( S(t) \) susceptibles, \( I(t) \) infected, and \( R(t) \) recovered persons with \( N = S + I + R \) the total (constant) population. Initially, let infected persons shed droplets of a single diameter \( d \), taken to be the droplet post-evaporation diameter. Moreover, let \( c \) be the (average) number of contacts a susceptible has per unit time with any individual. Since susceptibles and infected persons are homogeneously mixed a fraction \( I/N \) of these contacts will be with infected individuals. The expected number of contacts a susceptible has with infected individuals in a short time \( \delta t \) is \( c(I/N)\delta t \). However, the infectious agent is not the infected individual, but the pathogen carried by the droplet. According to the extended homogeneous mixing assumption each infected is surrounded by a personal cloud containing an average number of \( n_d = D/I \) droplets within a characteristic personal-cloud volume \( V_{cl} \), where \( D(t) \) is the total number of airborne droplets: the average droplet concentration per infected becomes \( n_d/V_{cl} \). The contact of a susceptible with a droplet occurs by inhaling: if \( B \) is the average breathing rate \( (m^3 s^{-1}) \) the average number of droplets per infected person encountered by a susceptible per unit of time is \( B (n_d/V_{cl}) \). Finally, let \( \tau_d \) be a characteristic time of breathing during contact rendering \( B(n_d/V_{cl})\tau_d \) the average number of droplets inhaled by a susceptible during the encounter. As each droplet is independent and the droplet population is randomly mixed, the number of contacts a susceptible has with a pathogen-carrying droplet becomes

\[
c = \frac{I}{N} B \frac{n_d}{V_{cl}} \frac{\tau_d}{\delta t} = c \frac{B}{V_{cl}} \frac{\tau_d}{\delta t} = \tilde{c}_d \frac{D}{N} \delta t,
\]

where \( \tilde{c}_d = cB\tau_d/V_{cl} \) is the contact rate of a susceptible with a droplet. Given the number of contacts between a susceptible and a droplet and the independence of the number of contacts the transmission term in the dynamical equations of the SIR model may be easily derived. For completeness we reproduce the derivation, as the matical equations of the SIR model may be easily derived.

\[
\frac{dS}{dt} = -\beta_d q_d(d) D S,
\]

where \( \beta_d = \tilde{c}_d \tilde{\sigma}_d \) is the transmission rate per droplet with \( \tilde{\sigma}_d \) the probability that a contact with an inhaled droplet results in successful transmission. Disease transmission depends indirectly on droplet size: airborne droplets transmit the pathogen from ambient air to the respiratory tract through inhalation and deposition. Thus, the probability of disease transmission depends on the pathogen load of the droplet and on its deposition location in the respiratory tract. The probability of transmission may, thus, be expressed as

\[
\tilde{\sigma}_d = p_d q_d(d) N_p(d),
\]

where \( p_d \) is the probability of transmission per inhaled pathogen, \( N_p(d) \) is the number of pathogens in a droplet of diameter \( d \), and \( q_d(d) \) is the probability of deposition in the human respiratory tract (a function of droplet size). The number of pathogens in a droplet is \( N_p(d) = V_d \rho_p \), where \( V_d \) is the (spherical) droplet volume and \( \rho_p \) the pathogen concentration in the lung fluid. Therefore, equation (2.2) becomes

\[
\frac{dS}{dt} = -N_p(d) \beta_d q_d(d) D S/N,
\]

where the transmission rate per inhaled pathogen is \( \beta_d = \tilde{c}_d \tilde{\sigma}_d \). Henceforth, the subscript \( d \) will denote airborne droplets.

Disease transmission via settled (deposited) droplets \( C(t) \) (of diameter \( d \)) is governed by an equation similar to equation (2.4). Specifically, we associate an average number \( n_c = C/I \) settled droplets with every infected individual. Let the settled-droplet removal rate by physical transport of a settled droplet to the upper respiratory tract be \( \eta \), a rate corresponding to the droplet removal rate due to inhalation \( B/V_{cl} \). The characteristic contact time \( \tau_c \) is the time associated with hand-to-face contact. Henceforth, the subscript \( c \) will refer to settled droplets. Then, the number of contacts a susceptible has with a settled droplet in \( \delta t \) is \( c \beta_c \tau_c \), where \( \beta_c \) is the deposition probability per inhaled pathogen \( \tilde{\sigma}_d \tilde{\pi}_d \). The transmission rate per settled droplet becomes

\[
\frac{dS}{dt} = -N_p(d) \beta_c q_c(d) D S/N,
\]

where \( \beta_c = \tilde{c}_c \tilde{\sigma}_c \tilde{\pi}_c \) is the transmission rate per settled pathogen. The characteristic time of contact \( \tau_c \) is the time associated with hand-to-face contact. Henceforth, the subscript \( c \) will refer to settled droplets. Then, the number of contacts a susceptible has with a settled droplet in \( \delta t \) is \( c \beta_c \tau_c \), where \( \beta_c \) is the deposition probability per inhaled pathogen \( \tilde{\sigma}_d \tilde{\pi}_d \). The transmission rate per settled droplet becomes

\[
\frac{dS}{dt} = -N_p(d) \beta_c q_c(d) D S/N,
\]

Note that the transmission rates per pathogen \( \beta_d \) and \( \beta_c \) do not depend on droplet size: they have been expressed as the product of a contact rate times the probability of infection per contact with the infectious agent, as in usual epidemiological SIR models.
If infected persons recover at a rate $\mu_I$, with $1/\mu_I$ the infectivity period, their dynamics is determined by

$$\frac{dI}{dt} = N_p(d)\beta_i q_i(d) D + \beta_c q_c(d) C \frac{S}{N} - \mu_I I,$$

$$\frac{dS}{dt} = -\frac{dS}{dt} - \mu_I I. \quad (2.6)$$

The dynamics of airborne droplets $D(t)$ is determined by the competition of generation and annihilation processes. Their number increases proportionally to the number of infected persons at the rate $\kappa$ pathogen-loaded droplets are shed. It decreases proportionally to their gravitational settling rate $\theta$. They are removed by inhalation, and subsequent deposition, via two processes: either each infected person breathes her/his own droplet cloud or any host encounters an infected person and she/he inhales the cloud droplets. The first removal-rate term, independent of the contact rate, is the product of the breathing rate $B$, times the average droplet concentration $n_I(V_c)$, the deposition probability $q_i(d)$, and the number of infected persons $I$: it evaluates to $Bq_i(d)D/V_c$. The removal rate due to an encounter of, say, a susceptible with an infected individual is proportional to the contact rate of a susceptible with a droplet $\tilde{c}_i$, the probability of encountering an infected I/N, the deposition probability $q_i(d)$, and the average droplet number per infected $n_I$: it evaluates to $\tilde{c}_i q_i(d) D/N$. Note that the droplet-inhalation removal term (per susceptible) differs from the corresponding infection term $N_p(d)\tilde{c}_i n_I q_i(d) D/V_c$ in equation (2.5). They differ because the rate of decrease of $D$ due to inhalation does not depend on the number of pathogens in the droplet: disease transmission depends on the pathogen load, but the droplet removal depends on its physical properties (e.g. droplet diameter). Furthermore, the rate of decrease of $D$ due to inhalation does not depend on the probability of infection: regional deposition in the lung differs from infection. The corresponding total removal rate is multiplied by the number of susceptibles. The same term describes removal by infected or recovered individual inhalation if we consider that the contact rate is the same for all hosts, and that $I \geq 1$. Then, the removal term due to encounters of all subpopulations becomes $\tilde{c}_i q_i(d) D \tilde{c}_i q_i(d) D$, i.e. it reduces to a linear term for a constant population.

Droplets are effectively removed because pathogens lose infectivity. If $\mu_d$ is the rate at which pathogens lose infectivity, i.e. $dN_p(d)/dt = -\mu_d N_p(d)$, then the rate droplets are removed is $\mu_d D$ since the number of pathogens is proportional to the number of droplets (for a constant pathogen concentration in the lung fluid, and $\mu_d$ independent of droplet size).

Therefore,

$$\frac{dD}{dt} = \kappa I - \left[ \left( \frac{B}{V_c} + \tilde{c}_i \right) q_i(d) + \mu_d + \theta \right] D. \quad (2.7)$$

In a completely analogous manner *mutatis mutandis* the number of settled droplets $C(t)$ changes according to

$$\frac{dC}{dt} = \theta D - \left[ (\eta + \tilde{c}) q_c(d) + \mu_c \right] C,$$

where droplets settled on surfaces lose infectivity at rate $\mu_c$, and their number increases at the rate $\theta$ airborne droplets settle. As in the case of airborne-droplet removal due to inhalation (and deposition), settled droplets may be removed by any infected, corresponding to a removal term $\eta q_c(d) C$, or following contact of any host with an infected, leading to a removal term $\tilde{c}_i q_i(d) C$.

The rate of change of the number of persons who recover is

$$\frac{dR}{dt} = \mu_I I. \quad (2.9)$$

The system of equations (2.5)–(2.9) is solved with appropriate initial conditions.

### 2.2.2. Polydisperse droplet number distribution.

The emitted polydisperse distribution is divided into $l$ bins, each one characterized by an average droplet diameter $d_i$, an airborne droplet number $D_i(t)$, and a corresponding number of settled droplets $C_i(t)$. We consider that $d_j \geq d_i$ for $j \geq i$. The dynamics of the infection for such a discretized distribution is described by

$$\frac{dS}{dt} = -\sum_{i=1}^{l} N_p(d_i) \beta_i q_i(d_i) D_i + \beta_c q_c(d_i) C_i \frac{S}{N},$$

$$\frac{dI}{dt} = -\frac{dS}{dt} - \mu_I I, \quad (2.10a)$$

$$\frac{dD_i}{dt} = \kappa I - \left[ \left( \frac{B}{V_c} + \tilde{c}_i \right) q_i(d_i) + \mu_d + \theta \right] D_i + \sum_{j>i} \phi_{ij} D_j - D_i \sum_{j<i} \phi_{ji}, \quad i, j = 1, \ldots, l, \quad (2.10b)$$

$$\frac{dC_i}{dt} = \theta D_i - \left[ (\eta + \tilde{c}) q_c(d_i) + \mu_c \right] C_i + \sum_{j>i} \phi_{ij} C_j - C_i \sum_{j<i} \phi_{ji}, \quad i, j = 1, \ldots, l, \quad (2.10c)$$

and

$$\frac{dR}{dt} = \mu_I I, \quad (2.10d)$$

with appropriate initial conditions. In equation (2.10c) the last two terms are evaporation terms with $\phi_{ij}$, the evaporation rate of droplet $d_i$ to become droplet $d_j$; the penultimate term models the increase of $D_i$ droplets due to evaporation of all larger droplets $(j > i)$, and the last term its decrease via evaporation to smaller droplets. Similarly, for settled droplets, equation (2.10d), the same evaporation terms for settled droplets are denoted by $\phi_{ij}$. We neglect nonlinear processes that convert smaller droplets into larger ones by coagulation and the inverse process of droplet break-up.
3. THE CASE OF INFLUENZA

3.1. Respiratory droplet number distribution

Experimental measurements of the respiratory aerosol number distribution shed during sneezing and coughing are relatively scarce. The size and number of droplets generated can be very diverse (Knight 1980) and of significant inter-subject variability (Edwards et al. 2004). Nicas et al. (2005) summarized and critically evaluated three detailed experimental studies (Duguid 1946; Loudon & Roberts 1967; Papineni & Rosenthal 1997). They suggested the use of the experimental data by Loudon & Roberts (1967). We, as well as Atkinson & Wein (2008), follow their recommendation: in particular, we use the data reported in table I in Nicas & Sun (2006). It should be noted, however, that more recent experimental measurements by Morawska et al. (2009) and Chao et al. (2009) found significant differences from the Loudon & Roberts data; they also questioned the data by Yang et al. (2007).

For simplicity and illustrative purposes, we approximate the full droplet number distribution by a bimodal distribution. Furthermore, we consider two bimodal distributions: one to model respirable droplets, and hence airborne influenza transmission, and one to model inhalable droplets, and hence airborne transmission at close contact (neglecting, as mentioned earlier, droplet-spray transmission). Estimates of droplet sizes corresponding to these distributions may be obtained from their gravitational settling and evaporation rates. Evaporation, being a molecular process, is very fast (Nicas et al. 2005; Morawska 2006); for example, a 20 μm droplet evaporates to a 1 μm diameter droplet within 0.24 s (at 50% ambient relative humidity). Henceforth, we neglect droplet evaporation, and we follow Nicas et al. (2005) to take the post-evaporation diameter (approximately) half the pre-evaporation diameter.

The droplet residence time in air, and the importance of a droplet size in airborne transmission, is determined from its gravitational settling velocity (Drossinos & Housiadas 2006); for example, a droplet of \(d = 10 \, \mu m\) deposits (crosses a characteristic length of 1.5 m) within 8 min, whereas a \(d = 4 \, \mu m\) droplet deposits within 50 min. Consequently, and in accordance with Nicas et al. (2005), we consider that droplets larger than 10 μm do not remain airborne sufficiently long to become respirable. The size of each mode of the respirable droplet distribution was calculated by mapping experimental data (Nicas et al. 2005) to two sizes. Specifically, for a minimum pre-evaporation bin diameter \(d_{\min}\) and a maximum bin diameter \(d_{\max}\) the mean droplet diameter is obtained from the mean droplet volume corresponding to these bins, \(\bar{v} = \pi (d_{\max}^3 - d_{\min}^3)/(24(d_{\max} - d_{\min}))\). We chose the (pre-evaporation) pairs \((d_{\min}, d_{\max})\) to be (2,11.6) and (11.6,22) to obtain post-evaporation diameters \(d_1 = 3.89 \approx 4 \, \mu m\) (small respirable droplets) and \(d_2 = 8.08 \approx 8 \, \mu m\) (large respirable droplets).

This bimodal representation is consistent with regional deposition of inhaled droplets in the respiratory tract (Hinds 1999; Drossinos & Housiadas 2006). Droplets with \(d > 8 \, \mu m\) deposit almost exclusively in the extrathoracic region, whereas droplets with \(d < 4 \, \mu m\) may reach the alveolar region.

Inspirable droplets are droplets that settle relatively fast, but at close contact a fraction may be inhaled by a susceptible during his/ her first breath if the infected person faces the susceptible (Atkinson & Wein 2008). According to Nicas & Sun (2006), their diameter ranges from 10 to 100 μm. We consider that the inhalable droplet distribution consists of a mode characteristic of respirable droplets and a mode characteristic of inspirable droplets. We obtained their diameters as previously described; specifically, the respirable droplet diameter was calculated from the mean droplet volume corresponding to \(d_{\min} = 2\), \(d_{\max} = 22.4\) (table I, Nicas & Sun 2006), and the inspirable droplet diameter to \(d_{\min} = 22.4\), \(d_{\max} = 228\). We found the (post-evaporation) respirable-droplet diameter to be \(d_3 = 7.3 \, \mu m\) and the inspirable-droplet diameter \(d_4 = 74 \, \mu m\).

Droplet generation rates \(k\) are calculated by requiring (pre-evaporation) volume (hence, pathogen number) conservation. The number of emitted mean-volume-diameter droplets was calculated by ensuring that the total emitted droplet volume (corresponding to the chosen mapping of bins) is preserved. For the respirable droplet distribution emitted during a cough we found generation rates of pathogen-loaded droplets \(k_1 = 160\) (\(d_1 = 4 \, \mu m\)) and \(k_2 = 7.5\) (\(d_2 = 8 \, \mu m\)), whereas for the inhalable droplet distribution \(k_3 = 41.47\) (\(d_3 = 7.3 \, \mu m\)) and \(k_4 = 138.48\) (\(d_4 = 74 \, \mu m\)). Nicas & Sun (2006), in addition, argued that only 50 per cent of the emitted inspirable droplets enter the head airways region; we, thus, take \(k_2 = 69.24\) inspirable droplets per cough. The respirable-droplet generation rates are consistent with the emission of 470 droplets of post-evaporation diameter greater than 1 μm per cough, half of which have a diameter less than 20 μm (Nicas et al. 2005). Note that the total emitted lung-fluid volume in a cough is 0.044 cm³; the volume in the respiratory fraction 0.7 × 10⁻⁴ cm³ (approx. 1.5 × 10⁻⁴% of the total emitted volume), and the volume in the inhalable fraction 2.38 × 10⁻¹ cm³ (approx. 0.54%). The daily generation rates are obtained by considering a 200-fold increase for a sneeze (Nicas et al. 2005), and a total of 11 sneezes and 360 coughs per day (Atkinson & Wein 2008). They are reported in table 1.

3.2. Bimodal droplet number distribution

The model equations, equations (2.10a)–(2.10c), for a bimodal droplet number distribution, with \(d_3 > d_4\) and expressed in terms of droplet infectivities \(\mathbf{\beta}\), become

\[
\frac{dS}{dt} = -(\mathbf{\beta}_{d_1} D_1 + \mathbf{\beta}_{d_2} C_1 + \mathbf{\beta}_{d_3} D_2 + \mathbf{\beta}_{d_4} C_2) \frac{S}{N},
\]

\[
\frac{dI}{dt} = -\mathbf{\beta}_{d_1} I, \quad \frac{dI}{dt} = -\mathbf{\beta}_{d_4} I, \quad \frac{dI}{dt} = -\mathbf{\beta}_{d_2} I, \quad \frac{dI}{dt} = -\mathbf{\beta}_{d_3} I
\]

\[
\frac{dD_1}{dt} = \mathbf{\beta}_{d_1} I - \nu_{d_1} D_1, \quad \frac{dD_2}{dt} = \mathbf{\beta}_{d_2} I - \nu_{d_2} D_2, \quad \frac{dC_1}{dt} = \mathbf{\beta}_{d_1} I - \nu_{d_1} C_1, \quad \frac{dC_2}{dt} = \mathbf{\beta}_{d_2} I - \nu_{d_2} C_2
\]
Table 1. Parameter values for three model influenza epidemic scenarios. *All other parameters as in the epidemic scenario mediated by airborne respirable droplets.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\rho_0$</td>
<td>pathogen concentration in the lung fluid</td>
<td>$3.71 \times 10^6$ pathogens ml$^{-1}$</td>
</tr>
<tr>
<td>$c$</td>
<td>contact rate between a susceptible and an infected</td>
<td>13 per day</td>
</tr>
<tr>
<td>$B$</td>
<td>breathing rate</td>
<td>$24$ m$^3$ d$^{-1}$</td>
</tr>
<tr>
<td>$V_{cl}$</td>
<td>volume of the personal cloud of an infected person</td>
<td>8.0 m$^3$</td>
</tr>
<tr>
<td>$p_i$</td>
<td>probability of infection by an inhaled pathogen</td>
<td>0.052</td>
</tr>
<tr>
<td>$p_s$</td>
<td>probability of infection by a settled pathogen</td>
<td>$6.93 \times 10^{-5}$</td>
</tr>
<tr>
<td>$\eta$</td>
<td>removal rate of settled droplets by physical contact</td>
<td>72 per day</td>
</tr>
<tr>
<td>$q_{ih}(d)$</td>
<td>inhaled-droplet deposition probability</td>
<td>$q_{ih} = 0.88$, $q_{sh} = 0.99$</td>
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<tr>
<td>$q_{sf}(d)$</td>
<td>hand-to-face deposition probability</td>
<td>$q_{sf} = 0.35$</td>
</tr>
<tr>
<td>$\mu_l$</td>
<td>infection recovery rate</td>
<td>0.20 per day</td>
</tr>
<tr>
<td>$\mu_d$</td>
<td>inactivation rate of airborne pathogens</td>
<td>8.64 per day</td>
</tr>
<tr>
<td>$\mu_e$</td>
<td>inactivation rate of settled pathogens</td>
<td>2.88 per day</td>
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**epidemic mediated by airborne respirable droplets**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference</th>
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<tr>
<td>$d$</td>
<td>diameter (post-evaporation)</td>
<td>$d_1 = 4$, $d_2 = 8$ µm</td>
</tr>
<tr>
<td>$N_{p}(d)$</td>
<td>number of pathogens per droplet</td>
<td>$9.15 \times 10^{-4}$ ($d_1$), $8.20 \times 10^{-3}$ ($d_2$)</td>
</tr>
<tr>
<td>$\tau_{d1} = \tau_{d2}$</td>
<td>characteristic breathing time</td>
<td>20 min</td>
</tr>
<tr>
<td>$\tau_{c1} = \tau_{c2}$</td>
<td>characteristic hand-to-face contact time</td>
<td>15 s</td>
</tr>
<tr>
<td>$\beta_{d1}$</td>
<td>transmission rate per inhaled pathogen</td>
<td>0.027 per day</td>
</tr>
<tr>
<td>$\beta_{d2}$</td>
<td>transmission rate per inhaled droplet</td>
<td>$2.2 \times 10^{-5}$ ($d_1$), $2.2 \times 10^{-4}$ ($d_2$) per day</td>
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<tr>
<td>$\beta_{s1}$</td>
<td>transmission rate per settled pathogen</td>
<td>$1.13 \times 10^{-5}$ per day</td>
</tr>
<tr>
<td>$\beta_{s2}$</td>
<td>transmission rate per settled droplet</td>
<td>$3.6 \times 10^{-3}$ ($d_1$), $3.24 \times 10^{-8}$ ($d_2$) per day</td>
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<tr>
<td>$\kappa$</td>
<td>respirable-droplet production rate</td>
<td>$4.10 \times 10^5$ ($d_1$), $1.92 \times 10^4$ ($d_2$) per day</td>
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<tr>
<td>$\theta$</td>
<td>gravitational settling rate</td>
<td>$28.80$ ($d_1$), $113.2$ ($d_2$) per day</td>
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**epidemic mediated by airborne inspirable droplets**

<table>
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<tr>
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<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$d$</td>
<td>diameter (post-evaporation)</td>
<td>$d_1 = 7.3$, $d_2 = 74$ µm</td>
</tr>
<tr>
<td>$N_{p}(d)$</td>
<td>number of pathogens per droplet</td>
<td>$6.0 \times 10^{-3}$ ($d_1$), 6.4 ($d_2$)</td>
</tr>
<tr>
<td>$\tau_{d1}$</td>
<td>characteristic breathing time (respirable droplet)</td>
<td>20 min</td>
</tr>
<tr>
<td>$\tau_{d2}$</td>
<td>characteristic breathing time (inspirable droplet)</td>
<td>1.0 min</td>
</tr>
<tr>
<td>$\tau_{c1} = \tau_{c2}$</td>
<td>characteristic hand-to-face contact time</td>
<td>15 s</td>
</tr>
<tr>
<td>$\beta_{d1}$</td>
<td>transmission rate per inhaled pathogen</td>
<td>0.027 per day</td>
</tr>
<tr>
<td>$\beta_{d2}$</td>
<td>transmission rate per inhaled pathogen (inspirable)</td>
<td>$1.4 \times 10^{-3}$ per day</td>
</tr>
<tr>
<td>$\beta_{d3}$</td>
<td>transmission rate per inhaled respirable droplet</td>
<td>$1.4 \times 10^{-4}$ per day</td>
</tr>
<tr>
<td>$\beta_{d4}$</td>
<td>transmission rate per inhaled inspirable droplet</td>
<td>$8.9 \times 10^{-7}$ per day</td>
</tr>
<tr>
<td>$\beta_{s1}$</td>
<td>transmission rate per settled pathogen</td>
<td>$1.13 \times 10^{-5}$ per day</td>
</tr>
<tr>
<td>$\beta_{s2}$</td>
<td>transmission rate per settled droplet</td>
<td>$2.37 \times 10^{-8}$ ($d_1$), $2.53 \times 10^{-5}$ ($d_2$) per day</td>
</tr>
<tr>
<td>$\kappa$</td>
<td>droplet production rate</td>
<td>$1.06 \times 10^3$ ($d_1$), $1.77 \times 10^5$ ($d_2$) per day</td>
</tr>
<tr>
<td>$\theta$</td>
<td>gravitational settling rate</td>
<td>$94.40$ ($d_1$), $9.523 \times 10^3$ ($d_2$) per day</td>
</tr>
</tbody>
</table>

**epidemic mediated by settled inspirable droplets**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau_{c1} = \tau_{c2}$</td>
<td>characteristic hand-to-face contact time</td>
<td>20 s</td>
</tr>
<tr>
<td>$\beta_{s1}$</td>
<td>transmission rate per settled pathogen</td>
<td>$1.49 \times 10^{-5}$ per day</td>
</tr>
<tr>
<td>$\beta_{s2}$</td>
<td>transmission rate per settled droplet</td>
<td>$3.13 \times 10^{-9}$ ($d_1$), $3.33 \times 10^{-5}$ ($d_2$) per day</td>
</tr>
</tbody>
</table>
and
\[
\frac{dR}{dt} = \mu J,
\]  
(3.1e)
where we introduced the droplet decay times
\[
v_d^{-1} = (1 + c \tau_d) \frac{B}{V_d} q_d(d_i) + \mu_d + \theta_1,
\]  
(3.2a)
\[
v_c^{-1} = (1 + c \tau_c) \eta q_c(d_i) + \mu_c,
\]  
(3.2b)
\[
v_d^{-1} = (1 + c \tau_d) \frac{B}{V_d} q_d(d_2) + \mu_d + \theta_2,
\]  
(3.2c)
and
\[
v_c^{-1} = (1 + c \tau_c) \eta q_c(d_2) + \mu_c.
\]  
(3.2d)
In our simulations, we chose initial conditions \( S(0) = 10^3 \), \( I(0) = 1 \), \( D_j(0) = D_j(0) = C_j(0) = C_j(0) = R(0) = 0 \). As mentioned, evaporation terms have been neglected; note, however, that droplet dynamics is determined by the post-evaporation diameter (e.g. settling rate), whereas the pathogen load depends on the pre-evaporation diameter.

The basic reproduction number corresponding to equations (3.1), calculated as suggested by Diekmann et al. (1990), evaluates to \((\theta_1 + \theta_2) / (\mu_d + \mu_c)\). The pathogen load depends on the pre-evaporation diameter.

\[
R_0 = \sum \beta_i \frac{\kappa_i}{\mu_i} v_{d_i} + \sum \beta_c \frac{\kappa_c}{\mu_c} v_{c_i} + \sum \beta_i \frac{\kappa_i}{\mu_i} v_{d_i} + \sum \beta_c \frac{\kappa_c}{\mu_c} v_{c_i} = R_0^d + R_0^c + R_0^d + R_0^c.
\]  
(3.3)

The terms \( \kappa_i / \mu_i \) and \( \kappa_c / \mu_c \) \((i = 1, 2)\) are ratios of droplet generation rates (settled droplets are only generated by settling airborne droplets in this model) to the infection recovery rate; they represent the number of droplets generated by an infectious individual during his/her infectivity period. The last equality in equation (3.3) decomposes \( R_0 \) into the sum of four terms each one corresponding to a droplet class. For each class the basic reproduction number is the product of droplet infectivity, number of droplets generated during the infectious period, and average droplet decay time. A similar decomposition was proposed by Li et al. (2009) using a different model. This decomposition of \( R_0 \) allows the quantification of the contribution of each droplet class to the spreading of an epidemic; we shall use it to identify dominant transmission modes in §4.

### 3.3. Model parameters

In our model the transmission rates per droplet \( \beta_i = \tilde{c}_i p_i = B_i q_i(d) N_i(d) \) \((i = d, c)\) that depend on the transmission rates per pathogen \( B_i = \tilde{c}_i p_i = h B_i q_i(d) / V_d \) or \( \beta_c = \tilde{c}_c p_c = c \eta \tau_c p_c \) are derived quantities. The parameters required for their determination are presented in table 1.

The average contact rate \( c \) is taken to be 13 contacts per day (Mossong et al. 2008). We take the probability of infection per inhaled pathogen to be \( p_i = 0.052 \) and per pathogen originating from settled droplets \( p_c = 6.93 \times 10^{-5} \), as suggested by Li et al. (2009). From the same source, we take the pathogen concentration in the lung fluid to be \( \rho_p = 3.71 \times 10^6 \) pathogens/cm\(^3\) to obtain the number of pathogens per droplet-size class \( N_i(d) \). The average breathing rate per person \( B \) is approximately 1 m\(^3\)/h\(^{-1}\) (Hinds 1999). The volume of the personal cloud of an infected person \( V_d \) is estimated to be 2 m \( \times \) 2 m \( \times \) 2 m = 8 m\(^3\). The removal rate of settled droplets (per person) \( \eta \) is related to the rate a susceptible touches the face, e.g. nose picking, eye rubbing. It may be estimated from the number of hand contacts with a surface and self-inoculation, approximately 15 per hour (Nicas & Best 2008), assuming that these contacts occur for 16 h \(^{-1}\), and that the probability a surface-to-hand contact leads to the face of a susceptible is 0.3 (Li et al. 2009); this evaluates to \( \eta = 72 \) per day.

The average deposition probability in the respiratory tract is taken to be \( q_d(d_1) = 0.88 \) for small respirable droplets and \( q_d(d_2) = 0.99 \) for large respirable or inhalable droplets (Hinds 1999; Drossinos & Housiadas 2006). The deposition probability of settled droplets onto facial surfaces is taken to be \( q_c(d) = q_c(d) = 0.35 \), an estimate based on the efficiency of pathogen transfer from hand to face (Li et al. 2009).

The transmission rates depend crucially on the characteristic time scales of breathing at contact \( \tau_d \) or the hand-to-face contact time \( \tau_c \). We consider three possible epidemic scenarios distinguished by different characteristic time scales. These scenarios are discussed in detail in §4. We first consider an epidemic mediated by respirable droplets. The characteristic times of breathing and hand-to-face contact are taken to be independent of size, the breathing time during contact estimated to be \( \tau_d = \tau_c = 20 \) min, in agreement with Mossong et al. (2008), who examined number and duration of susceptible—infected person contact rates. The characteristic hand-to-face contact time is estimated by requiring that it is smaller than \( \tau_d \) and that it reflects the high inactivation rate of influenza virus on hands (a process not explicitly included in the model). Since virus survival on hands is of the order of a minute or even less (Bean et al. 1982; Schürmann & Eggers 1983) we take \( \tau_c = \tau_c = 15 \) s. As a second scenario we consider an influenza epidemic mediated by inhalable droplets. The breathing time associated with inspirable droplets is much smaller since inspirable droplets settle very fast, remaining close to the infected; they are inhaled in the first breath after generation. We, thus, take \( \tau_d = 20 \) min, \( \tau_d = 1 \) min retaining the hand-to-face contact time scales \( \tau_c = \tau_c = 15 \) s. The third scenario is an epidemic mediated by inspirable droplets: we retain the breathing time scales of the second scenario, \( \tau_d = 20 \) min and \( \tau_d = 1 \) min, but we increase the hand-to-face contact time, a quantity difficult to quantify, to \( \tau_c = \tau_c = 20 \) s. Table 1 summarizes the pathogen and droplet transmission rate for all three scenarios.

The infectivity period varies, depending on the severity of the infection. Although it differs for subclinically infected persons and persons with clinical symptoms, a period of 2–6 days is considered common in the natural history of influenza (Carrat et al. 2008). We chose an average of 5 days (\( \tau_p = 0.20 \) per day).

The droplet settling rates \( \theta \) were taken from Hinds (1999) and Drossinos & Housiadas (2006).
The inactivation rates $\mu_d$ and $\mu_c$, possibly droplet-size dependent, are taken to be independent of size. Early aerosol studies on influenza survival showed that the inactivation rate of influenza virus is on average approximately 8.64 per day (Hemmes et al. 1960). Virus survival studies on surfaces estimate influenza survival between 30 min and 8 h depending on the type of the surface (Bean et al. 1982). We chose an inactivation rate $\mu_d = 8.64$ per day of virus in airborne droplets, and an inactivation rate $\mu_c = 2.88$ per day of virus in settled droplets.

4. RESULTS

We explored the dynamics of three model influenza epidemic scenarios identified by their dominant transmission mode.

4.1. An influenza epidemic mediated by airborne respirable droplets

Figure 1 describes the model dynamics of an epidemic wave for an influenza outbreak lasting about 150 days using the parameters presented in table 1. The model reproduces the characteristic transmission dynamics of influenza by showing a typical epidemic wave of infected persons and the decrease of the susceptible population. The basic reproduction number $R_0 = 1.28$ is close to values empirically estimated for influenza (e.g. Wallinga et al. 2006; Yang et al. 2009). The epidemic starts right after initial contacts between susceptibles and virus-containing droplets shed by infected (source) persons. The number of infected persons increases, reaching a maximum after about 78 days, decreasing afterwards. The number of susceptibles decreases monotonically, reaching a steady state after about 150 days. Approximately 44 per cent of the population gets infected. The number of droplets exhibits a dynamical behaviour similar to the dynamics of infected persons. All classes peak at day 78, but their numbers differ significantly. Small settled and airborne droplets are much more numerous than large airborne and settled droplets.

The relative importance of each mode is also quantified in figure 1d, where the cumulative number of infected persons by each mode (proportional to the corresponding force of infection) is presented. Small airborne respirable droplets are the dominant transmission mode, followed by large airborne, and lastly by settled respirable droplets whether small or large. Even though small respirable droplets have low infectivity per droplet (proportional to the droplet volume) they have high impact in viral transmission because they are numerous and they remain airborne for long periods. Large respirable droplets are generated at a lower rate but their infectivity is high; however, they settle faster, becoming of secondary importance as a transmission mode. The infectivity of settled droplets, irrespective of whether they originate from small or large respirable droplets, depends strongly on the duration of contact between a pathogen and a susceptible, and therefore on the pathogen inactivation rate.
on the hands. Experimental studies suggest that the rate is high, rendering contact a transmission mode of negligible importance (Bean et al. 1982; Schürmann & Eggers 1983). It should be noted though that estimates of the pathogen inactivation rate on the hands are rare, partially inconsistent and differ by several orders of magnitude (e.g. Boone & Gerba 2007; Weber & Stilianakis 2008), indicating the need for consistent experimental work.

The relative importance of transmission modes may also be estimated by comparing the relative contribution of each droplet class to $R_0$. They evaluate to $R_{d1}^i = 0.11$, $R_{d2}^i \sim 10^{-4}$, $R_{c1}^i = 0.17$ and $R_{c2}^i \sim 10^{-4}$, confirming that the dominant transmission mode is small airborne droplets ($R_{d1}^i$) followed by large airborne droplets ($R_{d2}^i$). The contribution of settled droplets is almost non-existent. This scenario suggests that an influenza epidemic lasting a few months may be dominated by airborne transmission of respirable droplets.

### 4.2. An influenza epidemic mediated by airborne inspirable droplets

The possible contribution of inspirable droplets is investigated in this and the following model scenarios. Even though inspirable droplets remain airborne for a very short time, settling rapidly, they may be important for close-contact transmission due to their high pathogen load (large volume). In addition, settled inspirable droplets may be transferred to facial tissues to contribute significantly to increased transmission by contact, again due to their pathogen load.

The difference between this scenario and the previous one is, apart from the droplet sizes, the breathing time associated with inspirable droplets ($t_d^i = 1$ min). As argued, we take the inspirable-droplet breathing time to be shorter than the respirable-droplet breathing time at contact ($t_d^r < t_d^i$).

The simulation results show an epidemic characterized by faster dynamics with a peak on day 27 and $R_0 = 2.31$. This type of dynamics is common in closed populations such as schools, nursing homes, etc. (Stilianakis et al. 1998; Nishiura et al. 2009). The high transmissibility of inspirable droplets results in a strong epidemic wave with a higher attack rate (87%). Furthermore, the relative importance of transmission modes changes. The cumulative incidence, figure 2d, shows that the dominant transmission modes are attributable to inspirable droplets, first to airborne droplets ($R_{d1}^i = 0.82$) and then to settled ones ($R_{c1}^i = 0.79$). Large respirable droplets also contribute to the spreading of the epidemic ($R_{d2}^r = 0.70$), but not settled respirable droplets ($R_{c2}^r \sim 10^{-3}$).

### 4.3. An influenza epidemic mediated by settled inspirable droplets

Settled droplets provide an important transmission mode if the hand-to-face characteristic contact time is
increased from $\tau = 15$ to 20 s. The epidemic wave unfolds very fast with a peak at day 23 and lasts less than two months. The basic reproduction number $R_0 = 2.57$ is high but typical of outbreaks in closed populations. The dominant contribution to transmission modes arises from settled inspirable droplets ($R_{0c} = 1.05$), followed by airborne inspirable droplets ($R_{0d} = 0.82$) and by airborne respirable droplets ($R_{0} = 0.70$). As in all three scenarios considered herein settled respirable droplets do not constitute a transmission mode ($R_{0c} = 0$). These numerical results indicate that contact through settled droplets as a dominant mode of transmission is a dynamically possible scenario too. Comparison of the last two scenarios suggests that a very fast epidemic is characterized by the presence of three modes of transmission (except for settled respirable droplets) of varying relative importance.

5. DISCUSSION

The aim of this work was to develop an epidemiological model of infection by inhalable respiratory droplets able (i) to describe the dynamics of transmission by explicit consideration of the vector, taken to be respirable (droplet diameter $d \leq 10 \, \mu m$), inspirable ($10 \, \mu m < d < 100 \, \mu m$), or the corresponding settled droplets; (ii) to treat aerosol physical processes, such as release and persistence in the air, gravitational settling, evaporation, and, indirectly, regional deposition in the respiratory tract, and to couple the associated droplet dynamics to biological processes at the population level; and (iii) to provide a theoretical framework for the investigation of the relative importance of transmission modes of respiratory infections, such as influenza, and the associated control strategies. A decomposition of the basic reproduction number into the contribution of each droplet-size class allowed a quantitative assessment of the relative contribution of different modes to overall transmission. The model does not incorporate infectious disease transmission by droplet transmission (also referred to as droplet-spray transmission) associated with close expiratory events. It does, however, include transmission at close contact by inhalation of inspirable droplets.

The following three model influenza epidemic scenarios, differing in the characteristic times associated with breathing at contact and the hand-to-face contact time, were considered: an epidemic mediated only by airborne respirable droplets (long characteristic time scales), one mediated by airborne inspirable droplets (shorter breathing contact time), and one by settled inspirable droplets (longer hand-to-face contact time). Epidemics mediated predominantly by inspirable droplets, either airborne or settled, are characterized by fast dynamics (short-term epidemic) as observed in closed populations; close contacts are common and transmission modes such as inhalation of airborne inspirable droplets or contact with settled inspirable droplets provide a selective advantage. Long-term epidemics with low attack rates may be attributed to respirable droplets. Hence, numerical results suggest that epidemic duration is inversely proportional to the pathogen load of the droplet-size class associated with the dominant transmission mode.

Model results, and in particular the relative importance of transmission modes, depend on parameters that are, in general, difficult to estimate and for which experimental evidence is conflicting. Parameters such
as number distribution of expelled respiratory droplets and their pathogen load, pathogen inactivation rates on hands and surfaces, and pathogen removal rates from surfaces determine the speed and extent of an epidemic, modify the relative importance of transmission modes, and determine the severity of the epidemic. As such, they may have dramatic implications for the assessment of the importance of transmission modes, and far-reaching implications for control strategies.

Nevertheless, we note that a proper characterization of all physical and microbiological parameters is not necessarily needed. As model results provide information on population dynamics, such as observed duration of outbreaks, incidence, etc., the model can also be used to help quantify model parameters. In this way model-predicted information on population dynamics could complement some of the more difficult micro-scale quantifications, although it is essential that consistency with plausible ranges of the unknown micro-scale parameters is required.

The model can be used to provide an initial assessment of the impact of control strategies that block a specific mode of transmission. It may be used to evaluate control strategies that are based either on the use of masks with several levels of protection for different droplet sizes or on interventions with combinations of measures, such as the use of masks and antivirals.

We thank Balint Alfordy, Lorenzo Isella, Thomas P. Weber and Dieter Schenzle for useful discussions.

APPENDIX A

Let $p_0$ be the probability that a contact with a droplet results in successful disease transmission: the probability that transmission does not occur is $1 - p_0$. For homogeneously mixed populations, and by associating a personal cloud with each infected individual, the number of contacts of a susceptible with a pathogen-carrying inhalable droplet is $\tilde{c}_d D \tilde{b} t / N$ with $\tilde{c}_d = c B \tau_d / V_d$. Since contacts are independent the probability that a susceptible escapes infection by any of these contacts with infected droplets during $\delta t$ is $(1 - p_0)^{-D \delta b t / N}$. Therefore, the probability $\tilde{q}$ that transmission occurs is

$$\tilde{q} = 1 - (1 - p_0)^{-D \delta b t / N}.$$

For an infinitesimal time interval, $\delta t \to 0$, the probability becomes $\tilde{q} = -\tilde{c}_d D \ln(1 - p_0) \delta t / N$, and for a small probability of transmission ($p_0 \to 0$) the overall transmission probability becomes

$$\tilde{q} = c_d \tilde{p}_d D N \delta t \quad \text{for} \quad \delta t \to 0, \quad \tilde{p} \to 0,$$

or, equivalently, the transmission rate per susceptible is

$$\frac{d\tilde{q}}{dt} = c_d \tilde{p}_d D N.$$

Hence, the total rate of transmission to all susceptibles is

$$\frac{dS}{dt} = -\frac{1}{N} \tilde{p}_d D S,$$

with $\tilde{p}_d = \tilde{c}_d \tilde{p}_d$ the transmission rate. As expected equation (A.1) shows that airborne-disease transmission is frequency dependent, i.e. it is independent of population size. Such a description is appropriate for transmission where contacts are determined by social constraints, as, for example, for influenza transmission (Keeling & Rohani 2008).

REFERENCES


