Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Multi-route respiratory infection: When a transmission route may dominate

Caroline X. Gao⁴, Yuguo Li⁵, Jianjian Wei⁶,⁎, Sue Cotton⁴, Matthew Hamilton⁵, Lei Wang⁶, Benjamin J. Cowling⁷

Centre for Youth Mental Health, University of Melbourne, Parkville, VIC 3052, Australia
School of Public Health and Preventive Medicine, Monash University, 553 St Kilda Rd, Melbourne, VIC 3004, Australia
Orygen, Parkville, VIC 3052, Australia
Department of Mechanical Engineering, The University of Hong Kong, Pokfulam Road, Hong Kong, SAR 999077, China
Institute of Refrigeration and Cryogenics, and Key Laboratory of Refrigeration and Cryogenic Technology of Zhejiang Province, Zhejiang University, Hangzhou 310000, China
Zhejiang Institute of Research and Innovation, The University of Hong Kong, Hangzhou 310000, China
School of Public Health, The University of Hong Kong, Pokfulam Road, Hong Kong, SAR 999077, China

HIGHLIGHTS

• Droplet evaporation is considered.
• Each transmission route may dominate and the influential factors are revealed.
• Short-range airborne route and inhalation of medium droplets are highlighted.

GRAPHICAL ABSTRACT

The exact transmission route of many respiratory infectious diseases remains a subject for debate to date. The relative contribution ratio of each transmission route is largely undetermined, which is affected by environmental conditions, human behaviour, the host and the microorganism. In this study, a detailed mathematical model is developed to investigate the relative contributions of different transmission routes to a multi-route transmitted respiratory infection. The following transmission routes are considered: long-range airborne transmission, short-range airborne transmission, direction inhalation of medium droplets or droplet nuclei, direct deposition of droplets of all sizes, direct and indirect contact route. It is illustrated that all transmission routes can dominate the total transmission risk under different scenarios. Influential parameters considered include the dose-response rate of different routes, droplet governing size that determines pathogen content in droplets, exposure distance, and pathogen dose transported to the hand of infector. Our multi-route transmission model provided a comprehensive but straightforward method to evaluate the probability of respiratory diseases transmission via different routes. It also established a basis for predicting the impact of individual-level intervention methods such as increasing close-contact distance and wearing protective masks.

© 2020 Elsevier B.V. All rights reserved.
1. Introduction

The 2003 severe acute respiratory syndrome (SARS) epidemics, the 2009 H1N1 influenza (Swine Flu) pandemic, the 2015 Middle East respiratory syndrome – (MERS) epidemics and the ongoing coronavirus disease 2019 (COVID-19) global pandemic have all highlighted the importance of studying the transmission mechanism of respiratory infectious diseases (Riou and Althaus, 2020; Scalera and Mossad, 2009; Yu et al., 2004; Zumla et al., 2015).

Respiratory diseases are often simply assumed to be transmitted via “close contact”; however, the complex transmission mechanisms often involve with more than one transmission route including direct or indirect contact, large droplet, and airborne routes (Lemieux et al., 2007; Bridges et al., 2003; Roy and Milton, 2004; Tang et al., 2006; Tang and Li, 2019). There are also many physical (respiratory particles and droplets generation), virological (viral loading, survival, location of virus receptor, etc.), behavioural (exposure distance, frequency of handshaking and surface touching, etc.) and environmental factors (temperature, humidity, ventilation, etc.) that affect the transmission (Tang et al., 2006; Wei and Li, 2016).

Hence, respiratory infections may show various characteristics under different contact scenarios. For example, the airborne transmission was believed to play a leading role in the influenza outbreak on a commercial aircraft in 1977 in Alaska (Moser et al., 1979). Conversely, in an influenza H1N1 outbreak in a tour group in China, close contact was the most correlated factor with the transmission (Han et al., 2009). Conflicting evidence for transmission routes, like these two cases, is prevalent for almost all respiratory infectious diseases (Tang et al., 2006). Failure in understanding the complex multi-route transmission mechanisms leads to recommendations of more conservative intervention methods such as keep a distance rather than increasing intervention methods such as increasing the threshold distance for airborne transmission is defined by the World Health Organization (WHO) as 1.0 m (WHO, 2007). However, it is known that droplet nuclei over 5 μm may also easily suspend and disperse over 1.0 m to cause transmission of respiratory disease, depending on the surrounding airflow conditions (Morawska, 2006). Secondly, in some cases, airborne transmission was misinterpreted as merely long-range transmission (Lemieux et al., 2007), but the role of short-range airborne is quite important but usually ignored (Liu et al., 2017a). Thirdly, close contact transmission (Chapin, 1912; Wells et al., 1948) can occur via multiple routes including short-range airborne (Liu et al., 2017a), direct inhalation of droplets, deposition of droplets on facial membranes and secondary contact with droplets deposited on surfaces (Nicas and Jones, 2009; Weber and Stilianakis, 2008).

Combining all these factors, we define the following transmission routes for our study (see Fig. 1).

Long-range airborne transmission – occurs when the susceptible shares the same indoor environment with the infector. For our model, infectious agents are assumed to be evenly distributed and reach a quasi-static equilibrium in the indoor environment. Detailed airflow patterns in individual environments are not considered.

Respiratory close contact transmission (or direct spray route) - exposure to a susceptible individual within the exhalation jet of the infector. It includes three transmission mechanisms: (Riou and Althaus, 2020) the short-range airborne transmission: exposure to droplets or droplet nuclei with a diameter less than a cut-off size of 5 μm不可以 inhalation of medium droplets or droplet nuclei (d₅₀ - 100 μm in diameter); and (Yu et al., 2004) direct deposition of droplets of all sizes. Droplets larger than 100 μm cannot be inhaled but can cause infection by direct deposition on the mucous membrane; respiratory droplets can also deposit on the mucous membrane. Short-range airborne were considered distinct from direct inhalation, as larger droplets mostly deposit in the head airway, and small droplets or droplet nuclei penetrate deeper in the lower respiratory airways, which may have a different dose-response pattern. The relative facing orientation of the susceptible and the infector also affect exposure risk. In this study, we assumed that respiratory close contact transmission only occurs when the breathing zone of the susceptible are inside the respiratory zone of the infector.

Contact (or surface touch) transmission - is introduced by touching contaminated surfaces (indirect contract route) and direct contact with the infector’s hand. Surfaces can be contaminated by direct deposition of respiratory droplets as well as by the hand of the infector. Here we only considered non-porous room horizontal surfaces and special hand contaminated surfaces (desks, door handles, etc.).
2.2. Multi-route transmission model

Our multi-route model is developed with the capacity to be extended to evaluate infection risks in a location visiting network (Gao et al., 2016). We use $i$ to denote a susceptible individual visiting location $k$, with infectors $j = 1...N$. The total infection risk of individual $i$ in location $k$, $R_i$, can be calculated combining the Wells-Riley equation (Wells, 1955) and the dose-response model (Nicas, 1996):

$$ R_i = 1 - e^{-\left(\nu_k D_{sa} + \nu_k D_{in} - \eta_k D_{d} - \eta_k D_{n}\right)} $$

(1)

The effectiveness of the viral dose introduced by the various routes is potentially different (relates to the presence of virus receptors in different regions of the respiratory tract as well as facial membrane). Hence, we introduce three dose-response coefficients, namely, $\nu_k$, $\eta_k$, and $\eta_m$, to account for potential different dose-response rates via the airborne route, direct inhalation and exposure to facial membranes respectively. $D_{sa}$, $D_{in}$, and $D_{d}$ are exposure doses due to long-range airborne, short-range airborne, direct inhalation and direct deposition routes, respectively. $D_{sa}$ and $D_{in}$ are exposure doses caused by hand contact with contaminated surface and direct hand to hand contact between the individual and the infector. The detailed mathematical derivation for each transmission route is provided in S1 Supplementary Material, and here we outlined the final equations and important parameters.

2.2.1. Exposure dose from the long-range airborne route

$D_{sa}$ is calculated via estimating the steady-state concentration of droplet nuclei in room $k$ and calculating the cumulative deposition infectious dose in susceptible’s respiratory tract. We use $d_0$ to denote the original diameter of the drop when it was generated from the mouth, and $d_i$ to denote the diameter of droplet nuclei or residue (final size). Then the total exposure dose is a function of: droplet generation rate, $G_i$; the respiratory deposition rate of droplet nuclei, $E(d_i)$; pulmonary ventilation rate, $p$; exposure time of the individual in the location $t_i$; virus concentration in the respiratory droplet generated from the infector $j$ on the day $T$ of the course of infection $U(j,T)$; room volume, $V^k$; the air change rate (ACH) in the room, and particle loss rate due to the death in the air, $\chi$, and room deposition, $\chi_d$.

$$ D_{sa} = \frac{\nu p t_i^k}{6 V^k (\text{ACH}^k + \chi_a + \chi_d)} \sum_{j=1}^{N_k} d_i^3 G(d_i)E(d_i)U(j,T)dd_i $$

(2)

2.2.2. Exposure dose from the short-range airborne route

This risk is estimated differently due to its different transmission mechanism. We assume that breathing, talking, and coughing all generate a respiratory jet cone (see Fig. 1) with a spreading angle of $\alpha$. The concentration of droplet nuclei at distance $s_{ij}$ can be estimated based on initial concentration and dilution rate along the cone. $\eta_{sij}$ is the face-to-face contact exposure time of $i$ and $j$. The concentration dilution factor at the distance $s_{ij}$ is a function of the initial radius of the mouth open area, $R_0$ spreading angle $\alpha$ and distance between two individuals.

$$ D_{in} = \sum_{j=1}^{N_k} D_{in}^{ij} = \sum_{j=1}^{N_k} \frac{n \Delta t_i R_0}{6 s_{ij} \alpha} \int_0^{d_i} G(d_i)E(d_i)U(j,T)dd_i $$

(3)

2.2.3. Dose due to direct inhalation of medium droplets or droplet nuclei $D_{d}$

Medium-sized droplets also travel in the respiratory jet, with larger ones falling out of the respiratory jet before reaching the breathing zone of the susceptible individual and smaller ones following the flow of the respiratory jet. The total infectious dose introduced by droplets with diameter between $d_0$ and $d_{b\max}$ (largest breathable droplet)
can be calculated similarly as the short-range exposure of droplet nuclei. Similar to Eq. (3), we have:

\[
D_{fhm}^h = \sum_{j=1}^{N_h} \frac{n \Delta t \kappa_{fhm}}{2} \int_0^{a_{dm}} P(d_0, s_j, U) G(d_0) E(d_0) d_0^{1/2} L(j, T) \xi_{d_{fhm}}(d_0) dd_0 \tag{4}
\]

Different from Eq. (3), Eq. (4) has two additional parameters: \(\xi_{d_{fhm}}(d_0)\), virus concentration dilution factor in larger droplets; and \(P(d_0, s_j, U)\) - probability of droplets with an initial size of \(d_0\) to reach distance \(s_j\) before falling out of the respiratory jet at an initial speed \(U\). \(\xi_{d_{fhm}}(d_0)\) is introduced as large droplets were often generated in the oral cavity (Wei and Li, 2016), where antiviral substances are presented and viral load is often lower compared with smaller droplets generated from the lower respiratory tract, nasal cavity and pharynx. To simplify the modelling, we use a step function to represent \(\xi_{d_{fhm}}(d_0)\)

\[
\xi_{d_{fhm}}(d_0) = \begin{cases} 
\xi_{d_{fhm}}(d_0 > d_k) \\
1 & (d_0 \leq d_k) 
\end{cases}
\tag{5}
\]

\(P(d_0, s_j, U)\) is affected by the mouth opening size, initial velocity of the jet, and the room temperature and humidity, which was modelled by combing the buoyant round jet model and droplet evaporation and motion models (Wei and Li, 2015).

2.2.4. Dose due to direct deposition in the facial membranes

Following the respiratory jet, both large and small droplets have the possibility to directly on the susceptible’s facial membranes. This dose can be estimated as:

\[
D_{fh}^h = \sum_{j=1}^{N_h} \frac{\Delta \kappa_{fh} A_{fh}}{2} \int_0^{a_{dm}} P(d_0, s_j, U) G(d_0) E(d_0) d_0^{1/2} L(j, T) \xi_{d_{fh}}(d_0) dd_0 \tag{6}
\]

where \(A_{fh}\) is the area of facial membranes (surface area of the eyes, nostrils and lips).

2.2.5. Exposure dose from hand-surface contact (touch) route

The virus on indoor surfaces is assumed to come from two sources: deposition of respiratory droplet and touch by contaminated hands of the infector. We assume that virus is uniformly distributed on hands, handprint and hand contaminated non-porous surfaces. Virus dose exposed to surfaces can be written as follows:

\[
D_{hs}^h = (C_{fhs} + C_{hhs}) A_{hs} f_{hm} \sigma \eta_{hm} \tag{7}
\]

where \(C_{fhs}\) and \(C_{hhs}\) are the virus concentration in the hand of individual \(i\) by touching a droplet-contaminated and a hand-contaminated non-porous surface. \(f_{hm}\) is the frequency of the hand of touching facial membranes (eyes, nose and mouth), \(\eta_{hm}\) is the transmission rate of droplets from hand to facial membranes. \(A_{hs}\) is the contact area of hand to mucous membranes. By assuming that virus concentrations on those surfaces reach a steady-state, we have:

\[
f_{hm} = \sum_{j=1}^{N_j} \frac{d_j}{\lambda_{j} + \lambda_d} G(d_0) L(j, T) \xi_{d_{fh}}(d_0) dd_0 + \int G(d_0) L(j, T) \xi_{d_{hhs}}(d_0) dd_0 \tag{8}
\]

The dose introduced via touching a special hand-contaminated surfaces (i.e., door handles, desks), \(C_{hhs}\), can be estimated via first estimate virus concentration on infector’s hand, and then virus concentration on the surface and finally virus concentration on the susceptible’s hand. This is expressed as a function of the virus death rate on the surface, \(\lambda_d\), and on hands, \(\lambda_{j}\); the frequency of hand touching the surface, \(f_{hm}\), and facial membranes, \(f_{hm}\); virus transmission rate of between surface and hand per touch \(\eta_{hm}\) and the volume of contagious nasal discharge transported the infectors hands per touch of facial membrane \(V_{hm}\).

\[
C_{hhs}^h = \frac{\left(\frac{f_{hm} \sigma}{A_{hs}}\right)^2 f_{hm} V_{hm} \eta_{hhs}}{A_{hs} X_{ch}^2} \sum_{j=1}^{N_j} \int_{j}^{T} L(j, T) \tag{9}
\]

We used one additional parameter, \(\xi_{hhs}\), to denote the virus concentration dilution rate in nasal discharge relative to the concentration in respiratory droplets. Covering mouth or nose while coughing was not considered as probability of covering and the dose of introduced virus are hard to estimate.

2.2.5.1. Exposure dose from direct hand to hand route. Assuming the virus is uniformly distributed on hands. Virus dose exposed to hand can be written as follows:

\[
D_{hh}^h = \frac{A_{hhs} f_{hhs} f_{hhs} \eta_{hh}}{A_{hs} X_{ch}^2} \sum_{j=1}^{N_j} \int_{j}^{T} f_{hhs} f_{hhs} V_{hhs} \eta_{hhs} L(j, T) \tag{10}
\]

Here \(f_{hh}\) is the frequency of handshaking between \(i\) and the infector \(j\). \(\eta_{hh}\) is the virus transmission rate of a hand-hand touch.

2.3. Modelling parameters and evidence sources

Room settings are illustrated in Fig. 1. We consider a single room of 5 (length) × 5 (width) × 3 (height) m³, with a ventilation rate in the range of 0.5–10 air changes per hour (ACH). One susceptible and one infector share the room for 10 h with 1-h face-to-face exposure when the susceptible is exposed directly in jet cone created by infector’s respiratory activities. Exposure distances were evaluated between 0.5 and 1.5 m of this close contact exposure. Virus load detected from samples of nose and throat swabs of influenza infectors is approximated according to 2009 Swine flu (Alman et al., 2016) (see S2 in Supplementary Material). Data of respiratory droplet generation rate and size distribution is estimated based on the study by Duguid (Duguid, 1946) (see S3 in Supplementary Material). Large droplets viral dilution rate and cut-off size are largely unknown. In an unpublished data by Cowling and colleagues, only two positive samples were found in saliva swabs from all 53 confirmed influenza A or B infectors. To be conservative, we assume that the virus load dilution rate, \(\xi_{d_{hh}}(d_0)\), is 0.05 in respiratory droplets larger than \(d_k\). The travel distance and final size of respiratory droplets estimated using our droplet dispersion model are provided in S4 in Supplementary Material. Other parameters are listed in Table S1. Since droplet nuclei smaller than 5 μm in diameter are able to reach the pulmonary region (Fig. S2) during inhalation and will suspend in the air for a long period (Wei and Li, 2015), the threshold value of 5 μm diameter used as the cut-off size for airborne droplet \(d_k\). Sensitivity analyses were conducted with changing key impacting parameters. All modelling tasks were conducted using R version 3.6.1 (2019-07-05). Modelling codes are provided in the Supplementary R code.

3. Results

Infection risk and contribution ratios by different transmission routes were evaluated under different modelling parameters. Fig. 2 summarized results with the default modelling parameters, and five other scenarios when a certain transmission route dominates. Overall infection risk is highest in the scenario displayed in Fig. 2F, where all the dose-response coefficients are equal to 1, and the viral load in nasal discharge is the same as that in small respiratory droplets. This is only true when virus receptors are widely prevalent (in the facial membrane, oral/nasal cavity upper/lower respiratory tract) and nasal
discharge and saliva are as contagious as small droplets; contact route dominates the transmission.

Fig. 2E presents the scenario when there is no virus dilution in large droplets ($d_{\text{DG}} = 1$), and transmission is dominated by direct deposition. The virus concentration of different sized droplets remains unclear, although droplets smaller than 5 μm in diameter are proved important virus carriers for influenza (Milton et al., 2013; Lindsley et al., 2010).

In scenario Fig. 2D, when the dose-effect of direction inhalation is as high as airborne droplet inhalation ($\eta_{\text{in}} = 1$), transmission is dominated by direct inhalation; the total volume of medium-sized droplets is larger although there are more droplets (in number) generated.

When total exposure time in the room is the same as close-contact time, and larger droplets ($d_{\text{DG}} > 30 \mu m$) do not contain a high concentration of virus, the dominating transmission route is the short-range airborne transmission (Fig. 2C). When the face-to-face exposure time is shorter ($t_{\text{c}} = 0.5 \text{ h}$) and room ventilation is poor (ACH = 0.5), long-range airborne transmission dominates.

We also evaluated the role of $d_{\text{DG}}$ (cut-off size for airborne particle) and $d_{\text{DG}}$ (largest high viral-load droplet size) in impacting total infection risk (see Table 2). Total infection risk is higher with larger airborne cut-off size, particularly when the exposure distance is longer.

Another key impact factor is the largest high viral-load droplet size $d_{\text{DG}}$. As $d_{\text{DG}}$ becomes larger, total infection risk increases dramatically when exposed at a closer distance (e.g., when the exposure distance is 0.5 m, infection risk changed from less than 0.5 m to 1.0 m when $d_{\text{DG}}$ increased from 30 to largest droplet size). This is due to a higher contribution from direct droplet inhalation and large droplet deposition (see Fig. 3). Increasing exposure distance also reduces total risk by reducing direct droplet inhalation and deposition (Table 2 and Fig. 3).

Effect of ventilation rates on contribution ratios of the long-range airborne route is demonstrated in Fig. 4. In the long-range airborne transmission dominant scenario (face-to-face exposure time $t_{\text{c}} = 0.5$), with the increase of the air change rate from 0.25 (18.75 m3/h) to 10 ACH, the total infection risk decreases by ~40% (85% reduction in infection risk from the long-range airborne route).

We also conducted sensitivity analyses with variable dose-effect coefficients. When the dose-effect of mucous membrane transmission was assumed larger, direct hand-to-hand contact transmission became more critical, particularly when the virus concentration is also high in nasal discharge (see Fig. 5). Similarly, when the dose-effect coefficient of direct inhalation route is high, the infection risk is dominated by direct inhalation particularly when viral load is also high in larger droplets (see Fig. 6).

4. Discussions

Given the current coronavirus pandemic, this study provided a timely and novel approach in evaluation transmission mechanisms of respiratory infection. We first proposed a new definition of multi-route transmitted respiratory infection and developed a full mathematical model to evaluate contributions of each transmission route. We illustrated that each transmission route could dominate the total infection risk under different virological, environmental and behaviour settings. Importantly our findings dissipate the traditional dichotomy of respiratory infection being transmitted by either close-contact or airborne routes. All these factors should be taken into consideration conjunctively to design intervention methods.

Our model may also explain the inconsistencies of research on the role of airborne transmission in historical outbreaks (Tang et al., 2006; Moser et al., 1979; Han et al., 2009). The airborne transmission can be
dominant when the ventilation was poor. For example, in the 1977 Alaska aircraft influenza outbreak, all passengers were exposed to a constant coughing patient in an enclosed aircraft without ventilation for more than 3 h (Moser et al., 1979). However, when the ventilation rate is high, or room exposure time is short, the contribution of airborne transmission can be insignificant, such as in the influenza tour group outbreak in 2009 in China (Han et al., 2009).

Compared with the models previously developed (Nicas and Jones, 2009; Atkinson and Wein, 2008), our model provides substantial advancement in modelling the complex droplet evaporation, transportation and deposition process, which equipped us with the ability to distinguish between long-range and short-range airborne, direct inhalation and direct deposition transmission routes. Unlike other studies, we have also evaluated how the key parameters (e.g., dose-response coefficient of different routes, the exposure distance, room ventilation rate and viral-load in large droplets and nasal discharge) impact the total infection risk and the relative contribution from each route. This study also shed light on important factors to consider when evaluating transmission of a novel respiratory infection, such as the prevalence of virus receptors in different parts of respiratory tract and difference of viral load in lung fluid, sputum, nasal discharge, saliva etc.

Another important difference in our model compared to previous work is that we considered the evaporation process of the respiratory droplets as well as the airborne ability related to the final size rather

![Graphical representation of transmission routes](image)
than initial size. Respiratory activities generate a substantial number of droplets between 0 and 50 μm. Droplets with the initial diameter of 10 μm (with a volume 1000 times larger than a 1 μm droplet) will evaporate quickly to a diameter of about 3 μm, which can then penetrate the lower respiratory tract. Using an airborne cut-off size of da = 5 μm, about 60% of respiratory droplets generated (d0 = 15 μm) can be evaporated and suspended in the air and introduce long-and short-range airborne infection, which was largely underestimated in other studies.

Cut-off size is also a critical factor. WHO (WHO, 2007) employed 5 μm to divide airborne and large droplets, while Nicas et al. (Nicas et al., 2005) adopted 10 μm. The simulations by Xie et al. (Xie et al., 2007) and Wei and Li. (Wei and Li, 2015) suggested that droplets with an initial diameter up to 60 μm could all disperse in a patient ward. In reality, the airborne ability of droplets or droplet nuclei may not be a simple cut-off value, and it depends on many other factors such as the background room airspeed and its turbulence, thermal stratification and air distribution. Further studies are needed to model these factors to account for the long-range airborne transmission rate.

### 4.1. Strengths, limitations and further directions

This study has a few major strengths. Firstly, we have defined a theoretical simulation framework to access the role of different transmission routes. As understanding the exact transmission mode of a certain respiratory infection is the prerequisite to take effective control measures, the framework can provide guidance to inform policy.

Secondly, the model highlighted critical parameters that determine contributions of different transmission routes, which can shed light on priorities in epidemiological or experimental investigations of future outbreaks. Thirdly, the study has drawn attention to the contribution of the short-range airborne route in the transmission of influenza, and the importance of ventilation to reduce the risk of the long-range airborne route, which were often neglected in previous research. Fourthly, the model can be used to evaluate intervention methods such as increasing exposure distance, increasing ventilation rates and wearing masks via changing parameter setting of the simulation code. Lastly, we made all the simulation codes freely available in an open-access code-repository to empower further research on this topic.

Cut-off size for airborne route

| Exposure distance sij | Largest high viral-load droplet size (d0) | da = 5μm | 30 | 50 | 100 | 200 | 500 | Largest droplet size |
|----------------------|------------------------------------------|----------|----|----|-----|-----|-----|----------------------|
| 0.5 m                |                                          | 0.52     | 0.62| 0.66| 0.71| 0.74| 0.77| 0.97                 |
| 1.0 m                |                                          | 0.49     | 0.62| 0.66| 0.71| 0.74| 0.77| 0.97                 |
| 1.5 m                |                                          | 0.46     | 0.62| 0.66| 0.71| 0.74| 0.77| 0.97                 |

Note: other parameter settings were listed in Table 1.

Table 2

Overall infection risk during the 10-h exposure with varying exposure distance (sij), the largest high viral-load droplet size (d0) and cut-off size for airborne route (da).

Fig. 3. Effect of close-contact exposure distance on contribution ratios of different transmission routes. Note: parameter setting see Table 1.
Secondly, although we have differentiated possible dose-response difference between airborne droplets and larger inhalable droplets, we did not model their deposition coefficient in different regions of the respiratory tract, which can be a key impacting factor in total transmission. If the virus receptor only presented in the pulmonary region, all transmission routes except the airborne route would be overestimated as only particles less than 10 μm can penetrate the larger respiratory airways.

Thirdly, breathing was also not included in the droplet generation process in the current model, and initial respiratory jet velocity differences between respiratory activities were not considered. Further development is needed to allow the model to separately consider different types of respiratory activities, including breathing, talking and coughing.

Although we have used parameters of influenza for the model analysis (such as viral loads in different-sized droplets, mucus and saliva, and virus survival rate in air and on surfaces), this model can be easily adapted to model all multi-routes transmitted respiratory diseases such as COVID-19. The current multi-route transmission model will be further developed into a web user interface, which could facilitate easy comparisons of different respiratory infections, important influencing factors as well as effectiveness of intervention methods such as wearing masks.

Fig. 4. Effect of ventilation rates on contribution ratios of different transmission routes. Note: face to face exposure time 30 min and other parameter settings see Table 1.

Fig. 5. Contribution ratios of different transmission routes with varying dose-response coefficient for membrane exposure, $\eta_m$, and nasal discharge virus dilution rate, $\xi_{NM}$. Other parameters were set the same as listed in Table 1.
Parameters were set the same as listed in Table 1.

CRediT authorship contribution statement

Caroline X. Gao: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing - original draft. Yuguo Li: Conceptualization, Supervision, Writing - review & editing. Funding acquisition. Jianjian Wei: Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing - review & editing. Matthew Hamilton: Data curation, Writing - review & editing. Lei Wang: Data curation, Writing - review & editing. Benjamin J. Cowling: Conceptualization, Supervision, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This work was financially supported by the National Natural Science Foundation of China (51808488) and the Research Grants Council of Hong Kong’s Collaborative Research Fund (C7025-16G), the Fundamental Research Funds for the Central Universities, and the HKU-Zhejiang Institute for Research and Innovation (HKU-ZIRI) Seed Funding Programme.

Additional information

The online code of the multi-route transmission model is available at GitHub: https://carolinexgao.github.io/Multi-route/Simulation_submission.html

5. Conclusions

We have developed a multi-route mathematical model to distinguish contributions of each route in influenza transmission under different exposure settings. It is highlighted that the transmission mechanism is complicated, and all different transmission routes may dominate the total infection risks. Therefore, recommendations of individual-level interventions for influenza and other related respiratory illnesses should be guided by all virological, behavioural and environmental factors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2020.141856.

References

Altmann, B.L., Pfister, G., Hao, H., Stowell, J., Hu, X., Liu, Y., et al., 2016. The association of wildfire smoke with respiratory and cardiovascular emergency department visits in Colorado in 2012: a case crossover study. Environ. Health 15 (1), 64.
Atkinson, M.P., Wein, L.M., 2008. Quantifying the routes of transmission for pandemic influenza. Bull. Math. Biol. 70 (3), 820–867.
Bean, B., Moore, B.M., Sterner, B., Peterson, L.R., Gerding, D.N., Balfour Jr., H.H., 1982. Survival of influenza viruses on environmental surfaces. J. Infect. Dis. 146 (1), 47–51.
Brenkton, G., Gitterman, L., Hirji, Z., Lemieux, C., Gardam, M., 2007. Transmission of influenza a in human beings. Lancet Infect. Dis. 7 (4), 257–265.
Bridges, C.B., Kuehnert, M.J., Hall, C.B., 2003. Transmission of influenza: implications for control in health care settings. Clin. Infect. Dis. 37 (8), 1094–1101.
Carrat, F., Vergu, E., Ferguson, N.M., Lemaitre, M., Cauchemez, S., Leach, S., et al., 2008. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. Am. J. Epidemiol. 167 (7), 775–785.
CDC, 1996. Guidelines for Isolation Precautions in Hospitals. Hospital Infection Control Advisory Committee: Centers for Disease Control and Prevention.
Chapin, C.V., 1912. The Sources and Modes of Infection. John Wiley & Sons Inc, New York.
Chen, S.C., Chang, C.F., Liao, C.M., 2006. Predictive models of control strategies involved in influenza transmission under different exposure settings. Am. J. Epidemiol. 167 (7), 775–785.
Duguid, J.P., 1946. The size and the duration of air-carriage of respiratory droplets and droplet-nuclei. J Hyg (Lond) 44 (6), 471–479.
Gao, X., Wei, J., Lei, H., Xu, P., Cowling, B.J., Li, C.M., 2006. Building ventilation as an effective disease intervention strategy in a dense indoor contact network in an ideal city. PLoS One 11 (9), e0162481.
Gupta, J.K., Belser, J.A., Wadford, D.A., Pearce, M.R., Katz, J.M., Tumpey, T.M., et al., 2011. Influenza virus aerosol exposure and analytical system for ferrets. Proc. Natl. Acad. Sci. U. S. A. 108 (20), 8432–8437.
Han, K., Zhu, X., He, F., Liu, L., Zhang, L., Ma, H., et al., 2009. Lack of airborne transmission during outbreak of pandemic (H1N1) 2009 among tour group members, China, June 2009. Emerg. Infect. Dis. 15 (10), 1578–1581.
Harper, G.J., 1961. Airborne micro-organisms: survival tests with four viruses. J Hyg (Lond) 59, 479–486.
Lemieux, C., Brankston, G., Gitterman, L., Hirji, Z., Gardam, M., 2007. Questioning aerosol transmission of influenza. Emerg. Infect. Dis. 13 (1), 173–174 (author reply 4–5).
Lindsley, W.G., Blachere, F.M., Thevisli, R.E., Vishnu, A., Davis, K.A., Cao, G., et al., 2010. Measurements of airborne influenza virus in aerosol particles from human coughs. PLoS One 5 (11).
