Prediction of Potential Respiratory Tract Infection from SARS-CoV-2 Through Hand-to-face Contact Transmission

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Objective: The Ministry of Health of China reported a cluster of severe pneumonia cases of unknown etiology in Wuhan city, the cause of which was later identified as a novel coronavirus. However, the risk of infection through indirect transmission routes remains unclear.
Methods: A mathematical modeling approach was used to estimate the risk of infection through hand-to-face contact. The probability of infection for various routes of transmission through face-touching behavior was then calculated.
Results: The probabilities of infection through hand-to-mouth transmission from nonporous and porous environments had log-normal (LN) distributions with geometric means (GMs) of 0.0116 and 0.0002, geometric deviations (GDs) of 2.9822 and 3.5560, and medians of 0.0127 and 0.0002, respectively, while those through hand-to-nose transmission from nonporous and porous environments had LN distributions with GMs of 0.0006 and 0.0000, GDs of 43.2310 and 47.3372, and medians of 0.0009 and 0.0000, respectively. The probability of infection through hand-to-eye transmission from a nonporous environment had a beta distribution with $\alpha = 2.38803$, $\beta = 13.60457$, a minimum of 0.0045, a maximum of 0.9021, and a median of 0.1179, while that from a porous environment had a Weibull distribution with a scale parameter of 0.0030, a shape parameter of 1.323, and a median of 0.0023.
Conclusion: SARS-CoV-2 infection will occur through hand-to-face contact via contaminated environment.

Key words: SARS-CoV-2, hand-to-face contact, indirect transmission, mathematical model

INTRODUCTION

On January 3, 2020, the Ministry of Health of the People's Republic of China reported a cluster of severe pneumonia cases of unknown etiology or cause originating in Wuhan city, Hubei Province. The cause of these severe pneumonia cases was subsequently identified as a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) [1]. Coronavirus disease 2019 (COVID-19) became a designated infectious disease in Japan on February 1, 2020 [2], and quickly spread to Europe and the USA. The World Health Organization (WHO) declared the COVID-19 outbreak a pandemic on March 11, 2020 [3].

The Nagoya city government reported that a man and his wife in their 60s who had recently returned from a trip to Hawaii tested positive for SARS-CoV-2 on February 14 and 15, 2020, respectively. Subsequently, 28 secondary cases possibly infected at sports gyms where his wife had visited after their trip were detected from February 29 to the beginning of March in Aichi Prefecture [4]. Similar outbreaks were observed in March in sports gyms in Chiba Prefecture [5]. Indirect contact transmission via athletic equipment shared by the infector and susceptible persons was suspected over direct contact infection.

Regarding the modes of transmission of SARS-CoV-2, the virus seems to be transmitted mainly via respiratory droplets from sneezing, coughing, or exhaling [1]. The virus can also survive for several hours or more on high-touch surfaces such as tables and door handles [6, 7] Therefore, hand contact to facial membranes (i.e., the mouth, nose, and eyes) is considered a potential exposure route.

The purpose of this study was to estimate the infection probability via contaminated hand contact with the mouth, nose, or eyes using the model developed by Nicas and Best [8]. To my knowledge, such infection routes have not been directly examined in regard to SARS-CoV-2. Therefore, I reconsider infection routes through hand contact with environmental surfaces and subsequent contact with the oral, nasal, and conjunctival mucosa based on the information currently available.

MATERIALS AND METHODS

Model framework

I used the model that was originally proposed by Nicas and Best [8], and later modified by Beamer *et al.* [9]. I assumed a scenario in which an infector and a susceptible person occupied the same area for 30 minutes (called the "exposure period") before the infector leaves. The susceptible person was then assumed to

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remain in the same area for at least 30 minutes (called the "decay period").

Let $C_{surface}$ (pathogen/cm^2) denote the average viable pathogen density on an environmental surface, and let $A_{surface}$ (cm^2 per contact) denote the average environmental surface area per hand contact. The rate of hand contact with an environmental surface is $H_{surface}$ (contacts per minute), and f_{12} is the fraction of the pathogens on the touched surface area that are transferred to the hand. The subscript 12 represents transfer from the surface (1) to the hand (2).

The rates of contact with a surface area by the hand and their transfer efficiency have different values according to the type of material the surface is composed of (porous or nonporous), and are calculated as follows:

Rate of transfer from a surface to the hand (number of viral pathogen/min)
$= H_{surface,\,i} \times f_{12,\,i} \times C_{surface} \times A_{surface}$
(i = porous, nonporous)

Rate of transfer from the hand to a surface (number of viral pathogen/min)
$= H_{surface,\,i} \times f_{21} \times C_{hand} \times A_{hand}$
(i = porous, nonporous)

Rate of pathogen transfer to target membranes (number of viral pathogen/min)
$= f_{23} \times H_{orifice} \times C_{hand} \times A_{hand}$

For mathematical simplicity, I assume that A_{hand} is equal to $A_{surface}$. The solution equation for C_{hand} as a function of time t (minutes) under $C_{hand} = 0$ at time 0 is given as follows:

$$C_{hand}(t) = (H_{surface,\,i} \times f_{12,\,i} \times C_{surface}) / \lambda_{decay} \times [1 - \exp(-\lambda_{decay} \times t)]$$

where $\lambda_{decay} = \alpha_{dieoff} + H_{surface} \times f_{21} + H_{orifice} \times f_{23}$, and i = porous, nonporous.

The mean concentration of C_{hand} (t) over the period [0, T] is as follows:

$$\overline{C_{hand}(t)} = (1/T) \int_0^T C_{hand}(t)$$

Therefore, the expected dose D_T of viable pathogen transferred to a targeted orifice over the period [0, T] is given as the following expression:

$$D_T = H_{orifice} \times A_{surface} \times \overline{C_{hand}(t)} \times f_{23} \times T$$

The mean concentration C_{hand} (t) over the period subsequent to time T, [0, T_{decay}], is given as the following expression:

$$\overline{C_{hand},\,T_{decay}} = C_{hand}(T) / (T_{decay} \times \lambda_{decay}) \times [1 - \exp(-\lambda_{decay} \times T_{decay})]$$

The expected dose D_{Tdecay} of viable pathogen transferred to a targeted orifice over the period [0, T_{decay}] is given as the following expression:

$$D_{Tdecay} = H_{orifice} \times A_{surface} \times \overline{C_{hand},\,T_{decay}} \times f_{23} \times T_{decay}$$

The expected total dose D_{total} is the sum of D_T and D_{Tdecay}.

The infection risk R means a probability that an individual could develop infectious disease, and is assumed to be an exponential dose-response curve, as a dose-response model for SARS-Cov1 was fitted to an exponential model in a previous report [10];

$$R = 1 - \exp(-\alpha \times D_{total}).$$

The probability that a single pathogen can infect the host through the oral, nasal, and conjunctival mucosa is denoted α. The overall probability of infection was calculated using the Monte Carlo simulation with probability distributions for the input parameters; in total, 10,000 simulations were conducted. All analyses were performed using Microsoft Excel 2010 (Microsoft Corp., Seattle, WA) and Crystal Ball™ software (Oracle Corp., Redwood Shores, CA). The Anderson-Darling statistic was used as a test of fit for the distributions.

Parameters

As for the infectivity of SARS-CoV-2, the basic reproduction number (R_0) estimated by the WHO was between 1.4 and 2.5, which was slightly higher than the R_0 value of 1.4–1.6 for the influenza A virus subtype H1N1 virus that caused the 2009 flu pandemic. Regarding COVID-19, respiratory tract infection due to hand-touching to facial membranes has been considered, similar to influenza A, but the transmissibility remains unknown. Therefore, the environmental exposure and pathogen transfer parameters for influenza A were used.

The average viable pathogen density $C_{surface}$ was derived in the case of exposure to influenza A in a room based on the results reported by Nicas and Best [8]. The contaminated area around the infector (3.1×10^4 cm^2) was assumed to be a circle with a radius of 1 m. The $C_{surface}$ value on the contaminated area as a result of coughing by the infector was 28 $TCID_{50}$/cm^2 as calculated from the steady-state constant value.

Hand contact rates from environmental surfaces to facial membranes were derived from micro-activity data reported by Breamer *et al.* [9]. The $H_{surface}$ area was assumed to be the area of a fingertip (2 cm^2) for hand-to-eye contact and the area of 10 fingers (10 cm^2) for both hand-to-mouth and hand-to-nose contact. Environmental surfaces consisted of two surface types: porous and nonporous. The transfer efficiencies from the touched surface areas to the hands and from the hands to orifices were characterized by experimental data using MS2 phage parameters [9]. The values for these parameters are summarized in Table 1 [11–15].

The probability α that a single pathogen could infect the host through the oral and nasal mucosa was 5.7×10^{-5} based on dose-response data from human subjects exposed to influenza A virus through intranasal instillation [9]. Nicas and Best [8] and Beamer *et al.* [9]. estimated hand-to-eye contact with assuming that hand-to-eye infection was pathogen directly transmitted from the ocular surface to the nasal mucosa and respiratory tract via the nasolacrimal duct. Firstly, I estimated infection probability using the same probability α with other routes. Secondly, I estimated infection probability by the assumption that virus replication

Table 1 Parameters and values

		GM*	GSD*	Unit	Source
$H_{surface,\ nonporous}$	log-normal	4.1	1.6	contacts/min	(11)
$H_{surface,\ porous}$	log-normal	5.5	1.5	contacts/min	(11)
H_{mouth}	log-normal	0.18	3.3	contacts/min	(11)
H_{eyes}	log-normal	0.06	3.3	contacts/min	(6)
H_{nose}	log-normal	0.01	66.7	contacts/min	(6)
A_{hand}	point value	2 for eyes 10 for mouth and nose		cm^2	(6)

*log-normal distribution defined by geometric mean (GM) and geometric standard deviation (SD)

		Min*	Max*	Unit	Source
A_{eye}	uniform	0.1	2	cm^2	(9)
A_{nose}	uniform	0.1	10	cm^2	(9)
A_{mouth}	uniform	1	41	cm^2	(9)
$f_{12,\ nonporous}$	uniform	0.05	0.22	contact/min	(14)
$f_{12,\ porous}$	uniform	0.0003	0.0042	contact/min	(14)
f_{21}	uniform	0.05	0.22	contact/min	(14)
f_{23}	point value	0.339		contact/min	(14)
$\alpha_{dieoff,\ nonporous}$	point value	1.6×10^{-2}		fraction/min	(15)
$\alpha_{dieoff,\ porous}$	point value	2.0×10^{-3}		fraction/min	(15)

*uniform distribution defined by minimum (Min) and maximum (Max)

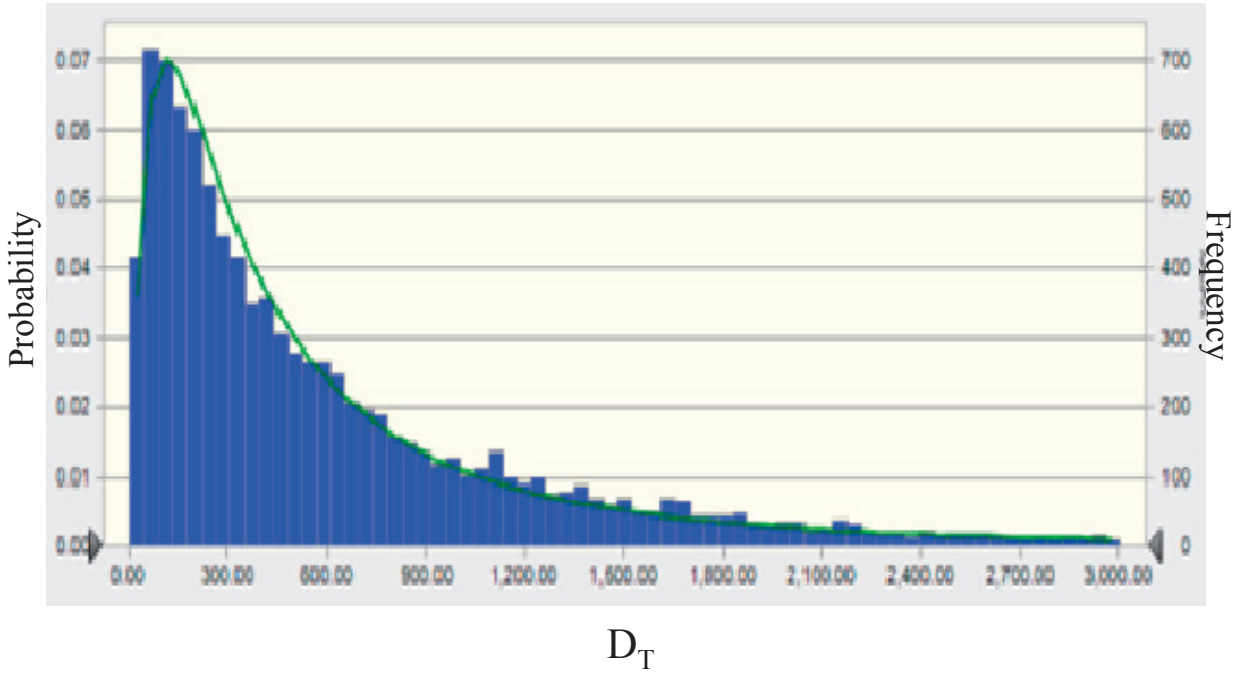

Fig. 1 The distribution of expected dose D_T for hand-to-mouth transmission from non-purus environment. (The line showed an lognormal distribution)

was occurred in the ocular tissues, as SARS-CoV-2 was suspected to cause an ocular tropism.

The probability α that a single pathogen could infect the host through the conjunctival mucosa was assumed from an *in vitro* model of ocular influenza viral infection using corneal tissue constructs. For the liquid inoculation in this experiment, a multiplicity of infection of 0.01 was equivalent to a virus titer of 750 PFU [16], and the virus titer PFU was converted to the infectious dose $TCID_{50}$. The probability α is associated with an infectious dose of 50% (ID_{50}) using the expression $\alpha = \ln(2) / ID_{50}$, where $ID_{50} \geq \ln(2)$, leading to $\alpha = 6.57 \times 10^{-4}$ per $TCID_{50}$ (see Appendix). As a result, $\alpha = 5.7 \times 10^{-5}$ per $TCID_{50}$ was used for hand-to-mouth and hand-to-nose contact. For hand-to-eye contact, $\alpha = 5.7 \times 10^{-5}$ per $TCID_{50}$ was firstly used, and secondly $\alpha = 6.57 \times 10^{-4}$ per $TCID_{50}$ was used for infection probability estimation.

RESULTS AND DISCUSSION

In this study, the estimated probability of infection was calculated for various routes of transmission through face-touching behavior for 30-minute exposure and decay periods. The expected dose D_T for

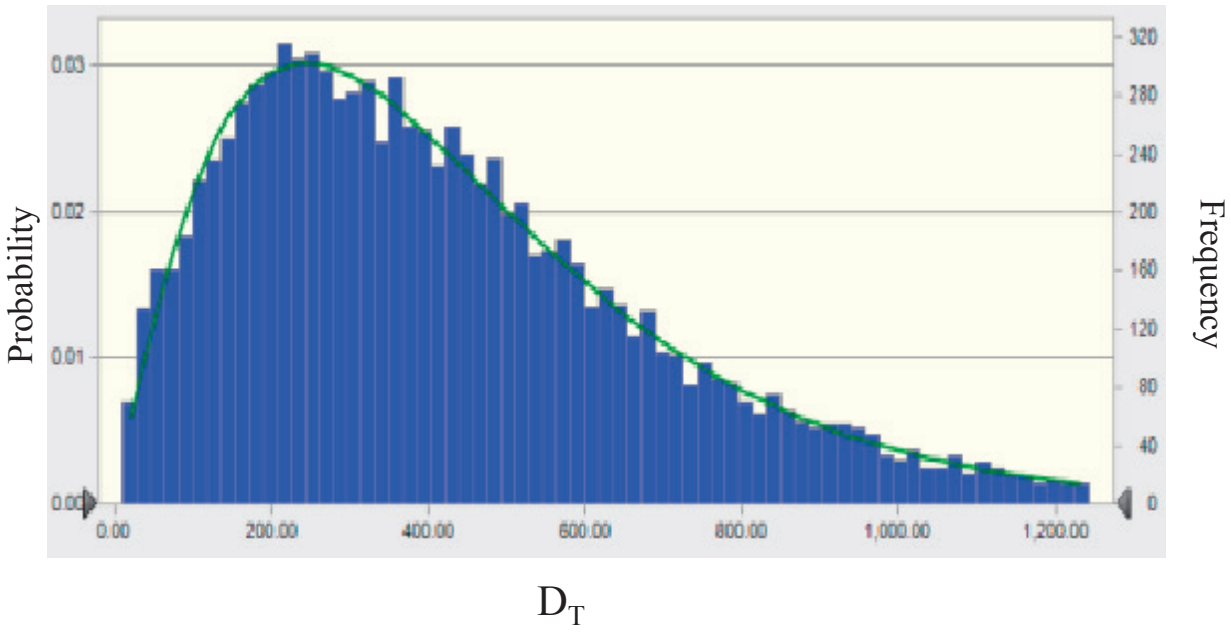

Fig. 2 The distribution of D_T for hand-to-eye transmission from non-porous environment. (The line showed a beta distribution)

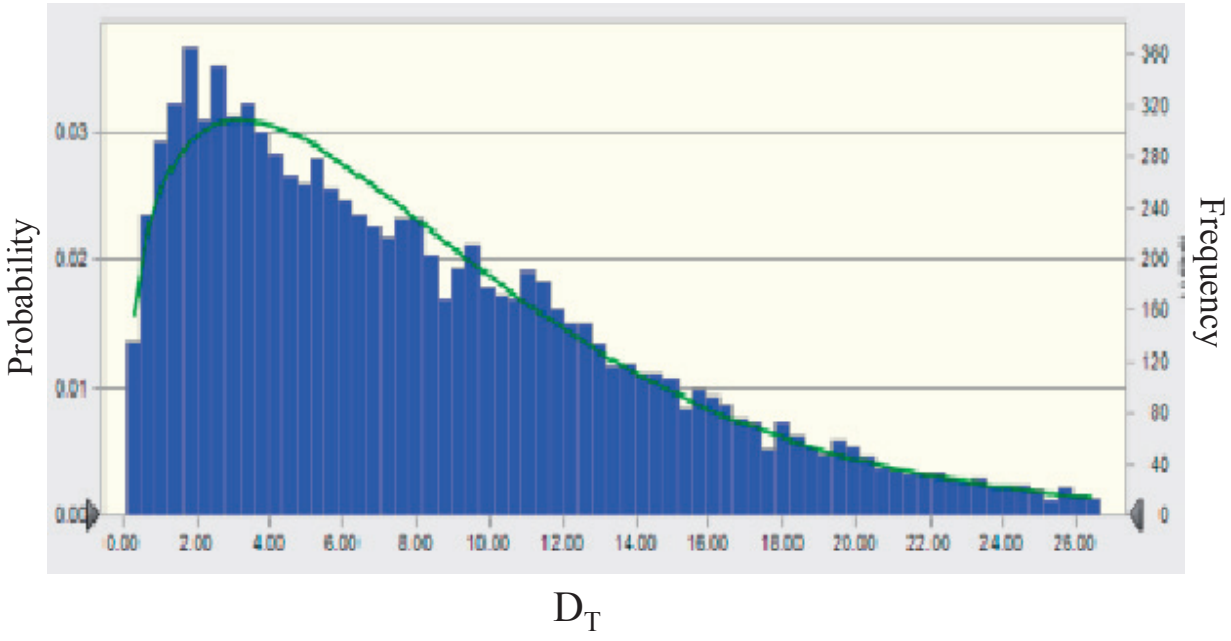

Fig. 3 The distribution of D_T for hand-to-eye transmission from porous environment. (The line showed a Weibull distribution)

hand-to-mouth transmission from nonporous environment was skewed positively, and was best fitted to the lognormal (LN) distribution by Anderson-Darling statistic (Fig. 1). On the other hand, the distribution of D_T for hand-to-eye transmission from nonporous environment was shown in Fig. 2, and was best fitted to a beta distribution (Fig. 2). The distribution of D_T for hand-to-eye transmission from porous environment was shown in Fig. 3 and was best fitted to a Weibull distribution (Fig. 3). The probability of infection had the same type distribution as the distribution of D_T for each route of transmission, and the distributions of the probability of infection were shown in the following with their location and shape parameters.

The probability of infection through hand-to-mouth transmission from a nonporous environment had an LN distribution with a geometric mean (GM) of 0.0116, a geometric deviation (GD) of 2.9822, and a median of 0.0127, while that from a porous environment had an LN distribution with a GM of 0.0002, a GD of 3.5560, and a median of 0.0002.

The probability of infection through hand-to-nose transmission from a nonporous environment had an LN distribution with a GM of 0.0006, a GD of 43.2310, and a median of 0.0009, while that from a porous environment had an LN distribution with a GM of 0.0000, a GD of 47.3372, and a median of 0.0000. Under the assumption that hand-to-eye transmission had the same infection probability of other routes, the probability of infection through hand-to-

eye from a nonporous environment had a beta distribution with $\alpha = 2.27306$, $\beta = 50.12863$, a minimum of -0.0002, a maximum of 0.2955, and a median of 0.0110, while that from a porous environment had a Weibull distribution with a scale parameter of 0.0003, a shape parameter of 1.32064, and a median of 0.0002.

Secondly, under the assumption that hand-to-eye transmission caused the ocular tropism, the probability of infection through hand-to-eye from a nonporous environment had a beta distribution with $\alpha = 2.38803$, $\beta = 13.60457$, a minimum of 0.0045, a maximum of 0.9021, and a median of 0.1179, while that from a porous environment had a Weibull distribution with a scale parameter of 0.0030, a shape parameter of 1.323, and a median of 0.0023.

Ratio of median probability for hand-to-eye transmission from nonporous vs. porous environment was 55.0 for upper respiratory route, and was 51.3 for ocular tropism, respectively.

Therefore, for each of three routes, the probability of infection from a nonporous environment was higher than that from a porous environment. Ratio of median probability for hand-to-eye transmission from nonporous vs. porous for upper respiratory route, was higher than that for ocular tropism.

Ong *et al*. [17] reported extensive environmental contamination by a SARS-CoV-2 patient with mild upper respiratory involvement in an isolation room before routine cleaning including twice-daily cleaning of high-touch surfaces. However, no environmental contamination was found in other patients' rooms after routine cleaning. Kampf *et al*. [6] described the persistence of coronaviruses on different types of inanimate surfaces and insisted that human coronaviruses can remain infectious from 2 hours to 9 days on different materials, as well as the inactivation of coronavirus by different types of biological agents. In addition, van Doremalen *et al*. [7] investigated the aerosol and surface stability of SARS-CoV-2, and found that it was more stable on plastic and stainless steel than on copper and cardboard; viable virus was detected up to 72 hours after application to these surfaces. These results suggest the possibility of indirect infection from the environment to facial membranes, and support the idea that SARS-Cov-2 was persistent during T_{decay} period.

Belser *et al*. [18] reviewed the capacity of influenza A to cause respiratory disease through the conjunctival mucosa. They reported that avian and human influenza A viruses, especially H7 viruses, can use the eyes as a portal of entry and cause ocular disease in humans. As for SARS-CoV-2 infection through the eyes, Lu *et al*. [19] reported that unprotected exposure can induce conjunctivitis several days before the onset of pneumonia. Seah and Agrawal [20] reviewed coronaviruses and ocular implications in humans and animals based on previous reports, and insisted that the possibility of SARS-CoV-2 infection thorough the eyes cannot be ignored. The higher ratio of median probability for hand-to-eye transmission from nonporous vs. porous for upper respiratory route, suggested that this route might be the more influenced by the type of environment.

The protective effects of handwashing in reducing the spread of influenza has been reported in several studies, and both hand-to-mouth and hand-to-nose contact are considered important routes of transmission. As for SARS-Cov-2 infection through hand-to-mouth and hand-to-nose contact, Giacomelli *et al*. [21] investigated olfactory and taste disorders in patients with COVID-19 and found that 12 (20.3%) of 59 patients were symptomatic before hospital admission. Although the likelihood of SARS-Cov-2 infection through the oral, nasal, and conjunctival mucosa is still unknown, these findings suggest that hand-to-mouth and hand-to-nose contact are both possible routes of transmission.

Cai *et al*. [22] investigated a cluster of COVID-19 cases associated with a shopping mall in Wenzhou, China. All patients except for those who worked on the same floor denied having direct close contact with other cases, but they shared common building facilities (e.g., restrooms, elevators). Therefore, the possibility of virus spread by indirect transmission was suggested.

This study did have some limitations. First, although the mode of transmission for SARS-CoV-2 is similar to that of influenza A, valid parameters to estimate the probability of SARS-CoV-2 infection were not available. Second, actual environments and surfaces are composed of complicated fractions of various materials, unlike those used in the present study.

The estimations calculated in this study and recent reports about SARS-CoV-2 suggest that the environment is a potential route of transmission, and emphasize the importance of proper hand hygiene and environmental disinfection. Further studies are needed to gather stronger evidence of definitive transmission pathways for SARS-CoV-2 infection.

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AUTHORS' CONTRIBUTIONS

Author had study idea, calculated the model, and wrote this paper.

CONFLICT OF INTEREST

There are no other conflicts of conflicts of interest to declare.

ETHICS AND CONSENT

Not required.

APPENDIX

As for a probability α for eye, data of human exposure was not available, and ocular infections of influenza and coronavirus have been shown *in-vitro* experiments and animal models. Thus, I used *in-vitro* infectivity data from the ocular influenza virus infection model with using corneal tissue under the condition that liquid inoculation dose at an multiplicity of infection (MOI) of 0.01, 0.01 MOI is corresponding to the value 750PFU in the influenza virus [16], and 750PFU is corresponding to the value 1071 $TCID_{50}$ from the expression $PFU = 0.7 \times TCID_{50}$. Consequently, 0.000647 was as the value for α obtained with using the expression $\alpha = \ln(2)/1071$ [16].

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