COVID-19 Transmission at Schools in Japan

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The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), remains a global public health concern in 2021. However, the risk of attending schools during the pandemic remains unevaluated. This study estimated the secondary transmission rate at schools using the results of a real-time reverse transcription-polymerase chain reaction (RT-PCR) screening test performed between July 2020 and April 2021, before starting the nationwide mass vaccination. A total of 1,924 students (20 RT-PCR-positive; 1.0%) from 52 schools or preschools were evaluated, together with 1,379 non-adults (95 RT-PCR-positive; 6.9%) exposed to SARS-CoV-2 in non-school environments. Assuming that the infectious index cases were asymptomatic and the transmission at schools followed a Bernoulli process, we estimated the probability of transmission after each contact at school as approximately 0.005 (0.5% per contact) with the current infection prevention measures at schools in Japan (i.e., hand hygiene, physical distancing, wearing masks, and effective ventilation). Furthermore, assuming that all children are capable of carrying the infection, then contact between an index case and 20-30 students per day at schools would yield the expected value for secondary cases of ≥ 1.0, during the 10 days of the infectious period. In conclusion, with the current infection prevention measures at schools in Japan, secondary transmission at schools would occur in approximately every 200 contacts. When considering this rate, compliance with the current infection prevention measures at schools and early detection and quarantine of the index cases would be effective in preventing the spread of COVID-19 at schools.

Keywords: basic reproduction number; coronavirus disease 2019 (COVID-19); school; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); transmission model
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Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is still the world's largest public health concern in 2021 (Rehman et al. 2021; Reid et al. 2021). As of April 2021, more than one-hundred million people have been infected with the disease, with more than 2 million deaths. The mainstay of the transmission mechanism of the disease is droplet infection (Meyerowitz et al. 2021); and a history of close contact with patients with COVID-19 is an established significant risk for acquiring the disease (Wang et al. 2020). Quarantine measures, vaccination, and infection prevention and control measures (such as masks, effective ventilation, social distancing, and broad screening tests for SARS-CoV-2, followed by contact tracing), are all important to suppress the pandemic (Kucharski et al. 2020).

From the early stage of the pandemic, the occurrence of cluster outbreaks based on unprotected high-density gatherings in a confined space (conferences, parties, and local events) has been thought to play a significant role in the spread of the disease in the community (Furuse et al. 2020). Meanwhile, the exact risk of attending schools, including preschools (kindergarten/nursery school), to acquire infection from other infected classmates, has not been widely evaluated. Without the evidence and rationale, healthcare policy making of closing or continuing schools in face to the nationwide or local spread of COVID-19 infection, and of performing screening tests upon an occurrence of an infected classmate for the contacted other classmates with the primary case, are difficult. In this study, we evaluated the risk of secondary transmission from an infectious child at schools in non-adults by analyzing the data of nasopharyngeal SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) swab test results from our testing center, stratified by the contact site (at schools/outside schools).

Methods

Enrollment

In this study, non-adults in the preschool/school ages (i.e., aged 0-18 years) who had a history of recent contact with COVID-19 patients at schools or other places were enrolled. For each tested individual, local governmental staff in public health centers checked the presence of clinical symptoms and the closeness of the contact. When needed, the individuals were guided to visit our testing center to undergo a screening RT-PCR test. We excluded individuals who were tested based on the presence of symptoms suggestive of COVID-19 with the absence of a recent contact history. This was because enrolling these individuals without a definite contact history would cause selection bias, making it difficult to estimate the exact secondary attack rate stratified by the contact levels and contact places.

All enrolled individuals were tested using nasopharyngeal SARS-CoV-2 RT-PCR swab tests at our drive-through testing center located in Japan between July 2020 and April 2021. This period was before the replacement of the major prevailing original virus strain in the locality by the N501Y variant in May 2021 and before starting COVID-19 vaccination for Japanese citizens. Moreover, during this study period, the accumulated proportion of infected individuals (i.e., previous cases of COVID-19) among non-adults in the locality was lower than 0.3%, based on the data released from the local government of Sendai City. Consequently, the whole tested population enrolled in this study could be presumed to be susceptible to the infection.

Evaluated variables

The enrolled non-adults (i.e., aged 0 to 18 years) with a recent contact history were divided into the following four subpopulations with different age groups: preschool age group (aged 0 to 6 years), elementary school age group (aged 6 to 12 years), junior high school age group (aged 12 to 15 years), and high school age group (aged 15 to 18 years). We obtained the RT-PCR test-positive rate with a 95% confidence interval (CI) for each age group after stratifying them by the places of contact. Furthermore, the crude rate of secondary transmission in each of the involved preschools/schools was obtained by dividing the number of RT-PCR test-positive students by the total number of the tested students in each preschool/school. In each preschool/school, the secondary attack rates per 10, 30, and 50 contacts were estimated. The estimated secondary transmission rates per 10, 30, and 50 contacts in each preschool/school were obtained using the data from preschools/schools with ≥ 10, 30, and 50 tested individuals with contact history at preschools/schools, respectively.

RT-PCR was performed by detecting the nucleocapsid protein set no. 2 (N2) gene, using the primer/probe set designed by the National Institute of Infectious Diseases in Japan (NIID_2019-nCoV_N_F2, R2, and P2) (Shirato et al. 2020). The reaction mixture comprised the primer/probe set for N2 detection, 4× TaqMan Fast Virus 1-Step Master Mix (Thermo Fisher Scientific, Waltham, MA, USA), and nuclease-free water. Details of the thermal cycling conditions have been previously reported (Ishii et al. 2021).

Closeness of contact

A history of close contact with COVID-19 patients in the tested individuals in non-school environments was judged by the local government staff in public health centers based on the fulfillment of all of the following four criteria: 1) contact with a COVID-19 patient from 2 days before to 14 days after the onset of symptoms or the positive RT-PCR test results; 2) not wearing masks; 3) contact involving < 1 m distance; and 4) ≥ 15 minutes of contact. Low-risk contact was defined as being in the same place as COVID-19 patients, with the absence of one or more of the four criteria for close contact.

Infection control measures performed at schools based on national guidelines

From the early stages of the pandemic in 2020, schools in Japan have implemented relatively uniform infection control measures at schools based on the health management manuals published by the Ministry of Education, Culture, Sports, Science and Technology in Japan (2020). Specifically, students are recommended to practice proper hand hygiene and maintain enough distancing (at least 2 m) from other students. When maintaining enough distancing is difficult, they are asked to always wear masks unless there is a risk of heatstroke. Furthermore, windows in two directions of the classrooms are recommended to be kept open or frequently (for several minutes more than once every 30 min) opened for effective ventilation. Such ventilation measures have been consistently implemented, even during the winter season in every school.

Preconditions of the COVID-19 spreading model at schools

For each contact at school, we assumed that the secondary transmission after each contact would follow an independent Bernoulli trial. That is, the outcomes after each contact at school (i.e., outcome in each Bernoulli trial following a binomial distribution) were considered to be binomial, either "transmitted" (i.e., success after a trial) or "not transmitted" (i.e., failure after a trial). Based on this premise, the number of secondary transmissions from the primary case in each day at a school was regarded to follow the binomial distribution of $f(x, n, p)$, where x is the specific number of successes (i.e., established number of secondary transmissions) in independent n trials (i.e., number of contacts by the index case at school), and p is the probability mass function for the secondary transmission rate at schools. Binomial distributions with different conditions in the number of trials and the level of probability mass were used to estimate the secondary transmission rate at school, by fitting the obtained distributions of the incidence of secondary transmission per specific times of contact in each preschool/school with these binomial distributions.

In this study, with the assumption that most of the symptomatic children will refrain from attending the school, probability mass functions of secondary transmission at schools with constant level (p) through the infectious period were adopted. In this study, based on the achieved estimated secondary attack rate per contact based on the data, three models with different levels of secondary transmission probability per contact at schools ($p = 0.001$, 0.003, or 0.005) were applied. By using these probability mass functions of p, the expected number of secondary transmissions (X) after n contacts with the primary case at a school in a specific single day can be achieved by calculating

$$E(X) = \sum_{x=0}^{n} \left(x \cdot f(x, n, p) \right)$$

Here, the probability mass function for the number of secondary transmissions from the primary case at a school, denoted as $f(x, n, p)$, follows the binomial distribution with parameters of x (the number of established secondary transmissions), $n \in N$ (total times of independent Bernoulli trial), and $p \in [0,1]$ (the probability mass for transmission per each contact at school).

$$f(x, n, p) = Pr(X = x) = \binom{n}{x} p^x (1-p)^{n-x}$$
$$X \sim B(n, p)$$

where $\binom{n}{x}$ is a binomial coefficient and $Pr(X=x)$ denotes the probability that the variable X is equal to a specific value of x. Theoretically, if the achieved $E(X)$ is < 1.0, the spread of COVID-19 transmission at a school is likely to be eventually extinct within several generations of transmission.

Statistical analysis

Comparisons of the RT-PCR test-positive rate between age groups with different types of schools were performed by the chi-square test or Fisher's exact test according to the size in each cell and the number of compared groups. Statistical significance was set at $P < 0.05$. The range of 95% CI for the RT-PCR test-positive rate in each group of different age groups was obtained. Drawing of the binomial distributions in different preconditions, statistical analyses, and spreading simulations in the present study were performed by using MATLAB R2015a (MathWorks, Natick, MA, USA) and R Statistical Software (version 4.0.5; R Foundation, Vienna, Austria).

Ethics

The Institutional Review Board of Tohoku University Graduate School of Medicine approved the present study (approval number: 2020-1-535). The review board waived the need for written informed consent to avoid the risk of spreading the infection at the testing center. Informed consent was secured in an opt-out manner.

Results

Participants and RT-PCR test results

A total of 3,303 non-adults in the preschool/school ages with a recent contact history with COVID-19 patients, who were tested at our drive-through RT-PCR swab testing center between July 2020 and April 2021, were enrolled in this study. Other tested cases without definite contact history (n = 2,927) or adult cases aged 18+ years with recent contact history (n = 2,690) were not enrolled. The numbers of individuals stratified by the contact locations and age groups (i.e., preschool age, elementary school age, junior high school age, and high school age) are shown in Fig. 1. RT-PCR test results and overall crude test-positive rates (95% CI) are listed in each subgroup in Table 1. In all age groups among non-adults, overall crude test-positive rates were significantly lower in those contacted at schools than in those with household contacts (Fisher's exact test, $p <$

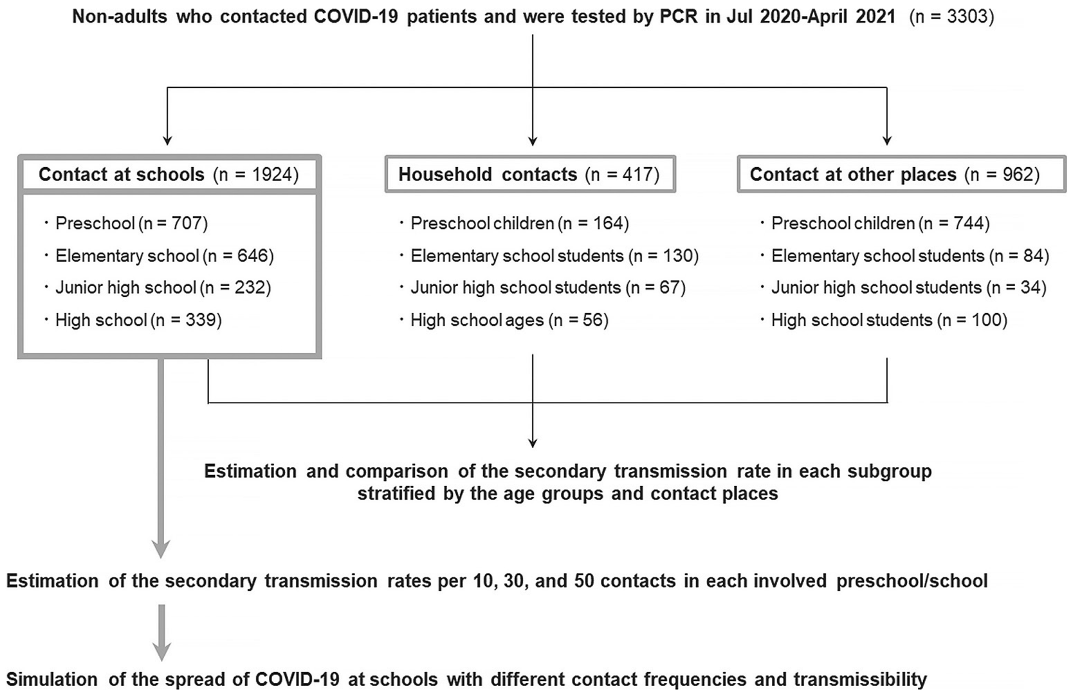

Fig. 1. Flow diagram of the study design.

Table 1. SARS-CoV-2 RT-PCR test positive rate in non-adults stratified by the place of contact.

	RT-PCR test-positive (n)	RT-PCR test-negative (n)	Crude test-positive rate (%; 95% CI)
Preschool (kindergarten/nursery school): aged 0-6 years			
Contact at preschools	9	698	1.27 (0.67-2.40)%
Household contacts	29	135	17.68 (12.60-24.24)%
Contact at other places (close contact)	5	86	5.49 (2.37-12.22)%
Contact at other places (low-risk contact)	9	644	1.38 (0.73-2.60)%
Elementary school: aged 6-12 years			
Contact at schools	5	641	0.77 (0.33-1.79)%
Household contacts	17	113	13.08 (8.33-19.95)%
Contact at other places (close contact)	0	43	0.00 (0.00-8.20)%
Contact at other places (low-risk contact)	0	41	0.00 (0.00-8.57)%
Junior high school: aged 12-15 years			
Contact at schools	0	232	0.00 (0.00-1.63)%
Household contacts	17	50	25.37 (16.49-36.93)%
Contact at other places (close contact)	1	18	5.26 (0.93-24.63)%
Contact at other places (low-risk contact)	0	15	0.00 (0.00-20.39)%
High school ages: aged 15-18 years			
Contact at schools	6	333	1.77 (0.81-3.81)%
Household contacts	9	47	16.07 (8.69-27.80)%
Contact at other places (close contact)	5	37	11.90 (5.19-24.99)%
Contact at other places (low-risk contact)	3	55	5.17 (1.77-14.14)%

The crude RT-PCR test-positive rate in each subgroup was calculated by dividing the overall number of individuals with RT-PCR test-positive results by the overall tested individuals in each subgroup.
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse transcription-polymerase chain reaction.

0.0001 for all age groups). The secondary transmission rate at schools was not statistically different among the four age groups (chi-square test, p = 0.1709).

Next, we evaluated the potential influence of the closeness of contact at schools on the secondary transmission rate and calculated the secondary transmission rate among the students with close contact at schools. The achieved rates in each age group were as follows: 1.0% among preschool children (1 positive test in 105 children), 1.2% among elementary school students (one positive test in 86 students), 0.0% among junior high school students (no positive tests in 26 students), and 4.9% among high school students (six positive tests in 121 students). These estimated secondary attack rates after close contact at schools (i.e., 0%-10%) were lower than those after household contact (i.e., 10%-30%) or after close contact outside schools (i.e., 0%-25%).

Secondary transmission rate in the evaluated schools/preschools

The cohort of the present study included 1,924 students from 52 schools/preschools who contacted an infected classmate at their schools/preschools. Among them, 20 (1.04 %, 95% CI: 0.67-1.60%) had positive RT-PCR test results. A histogram for the crude rate of RT-PCR test-positive results (i.e., the number of RT-PCR test-positive children divided by the number of whole tested children) for each of the 52 schools is shown in Fig. 2A. Among the 52 schools/preschools, 42 of them yielded no secondary transmission case. One of the high schools yielded an exceptionally high test-positive rate with 3 students with positive test results from 8 tested students, but these 3 students (37.5%) were confirmed to have had close contact with an infected classmate after school outside the school site. Thus, exclusion of this outlier does not bias the subsequent analyses. Histograms of the numbers of RT-PCR test-positive students per 10, 30, and 50 contacted children are shown in Fig. 2B-D. The distribution patterns of these his-

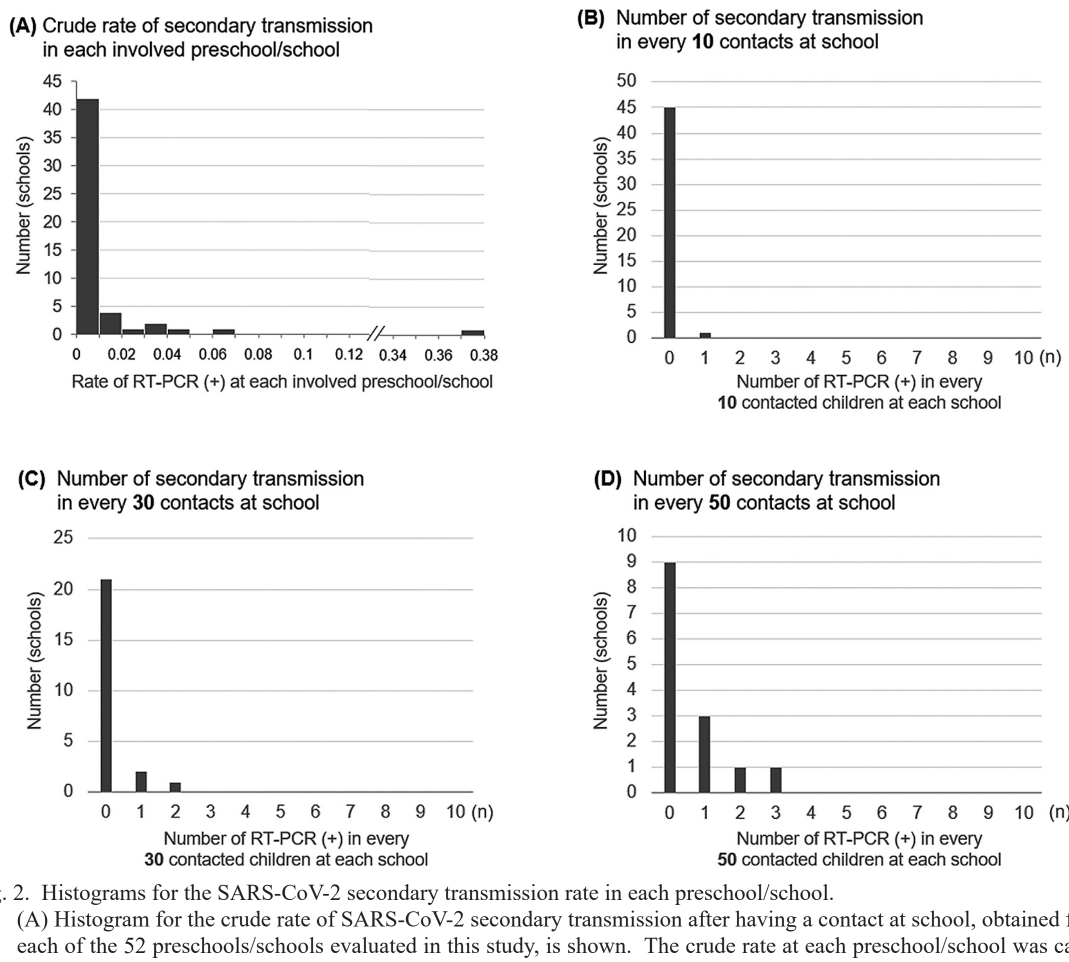

Fig. 2. Histograms for the SARS-CoV-2 secondary transmission rate in each preschool/school.
(A) Histogram for the crude rate of SARS-CoV-2 secondary transmission after having a contact at school, obtained from each of the 52 preschools/schools evaluated in this study, is shown. The crude rate at each preschool/school was calculated by dividing the number of RT-PCR test-positive children by the number of whole tested children after having a contact at preschool/school. (B-D) Histograms for the numbers of SARS-CoV-2 secondary transmission in every 10 (B), 30 (C), and 50 (D) contacts at school are shown.
RT-PCR, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

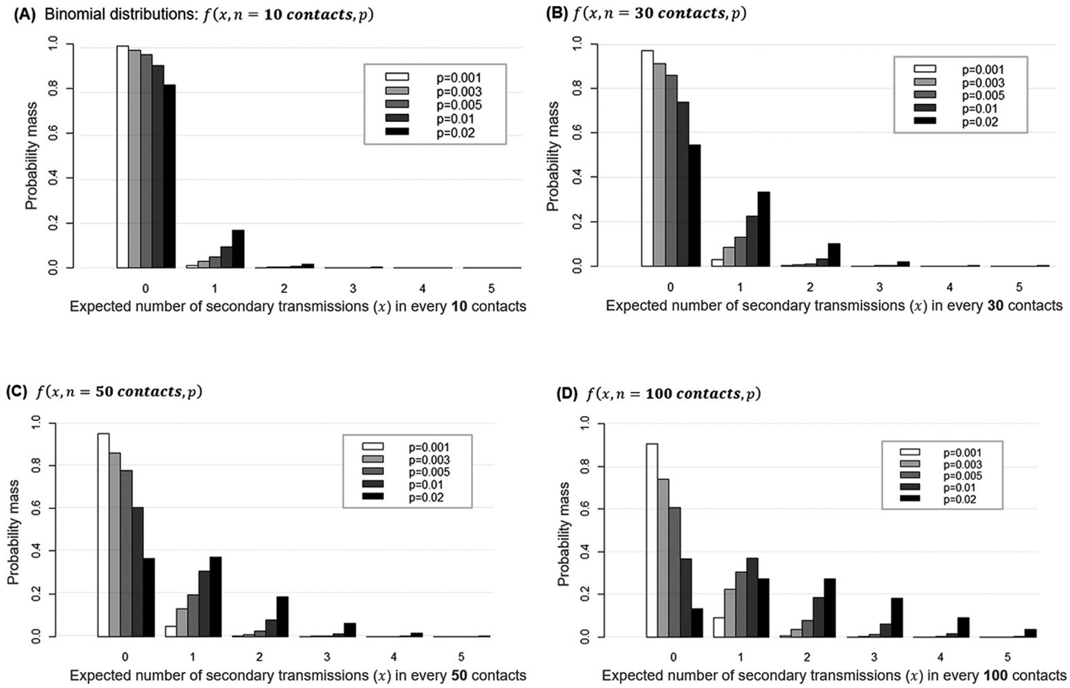

Fig. 3. Binomial distributions for the numbers of secondary transmissions with different contact frequency and transmissibility.
Binomial distributions for the expected numbers of secondary transmissions with different assumed transmissibility per contact at school (0.001, 0.003, 0.005, 0.01, or 0.02) in every 10 (A), 30 (B), 50 (C), and 100 (D) contacts are shown.

tograms suggest that the number of secondary transmissions at preschools/schools roughly follows a binomial distribution based on the Bernoulli trial in each contact, supporting the preconditions of the spreading models applied in this study.

To estimate the secondary transmission rate after each contact at preschool/school from these distribution patterns, binomial distributions for the expected number of secondary transmissions (x) with different assumed daily contact frequencies (n; number of contacts made by an index case at school) and probabilities of transmission per each contact (p) were generated (Fig. 3). Judging by fitting the patterns of the obtained histograms with these binomial distributions, the probability of secondary transmission per contact at school, regardless of the closeness of contact, was suggested to be approximately 0.005 (i.e., 0.5%) with the current infection prevention measures implemented at schools in Japan.

Simulation of infection spread at schools by asymptomatic children

Based on the estimated probability mass of 0.005 after each contact at schools, we calculated the expected value of the accumulated secondary attack rate ($E(X)$) at schools on each day during the infectious period of the index case (Fig. 4). Here, the actual secondary transmission rate could be lower, because some of the tested students could have made contact with the index case at school for more than one day. Thus, conditions with three different probabilities for secondary transmission per contact at school (p = 0.001, 0.003, and 0.005) and four different daily contact times at schools (10, 30, 50, and 100 contacts per day by the index case) were used for the spread simulations. When probabilities of 0.001, 0.003, and 0.005 are applied, the daily number of contacts by the index case greater than 100, 30, and 20, respectively, would produce an accumulated $E(X)$ value higher than 1.0.

Discussion

In this study, the probability of secondary transmission after each contact at schools with the current infection prevention measures implemented at schools in Japan was estimated to be approximately 0.005 (i.e., 0.5% per contact). In other words, secondary transmission at schools would occur approximately once with every 200 contacts at schools. This estimated secondary transmission rate at schools was much lower than the transmission rate in households or in other places, regardless of the closeness of contact at schools. As being simulated in this study, if screening tests or quarantine measures are not implemented to the index case, the expected value for the accumulated numbers of secondary transmission at the school throughout the infectious period will surpass 1.0, if the index case continuously makes more than 30 contacts with other students every day. Currently, the average number of students per each class at schools in Japan is around 30. Thus, unless the vaccination for COVID-19 prevailed among the non-adults and most of the students become insusceptible to the infection, restricting the opportunity of contact with other students at schools is a valid way of preventing the occur-

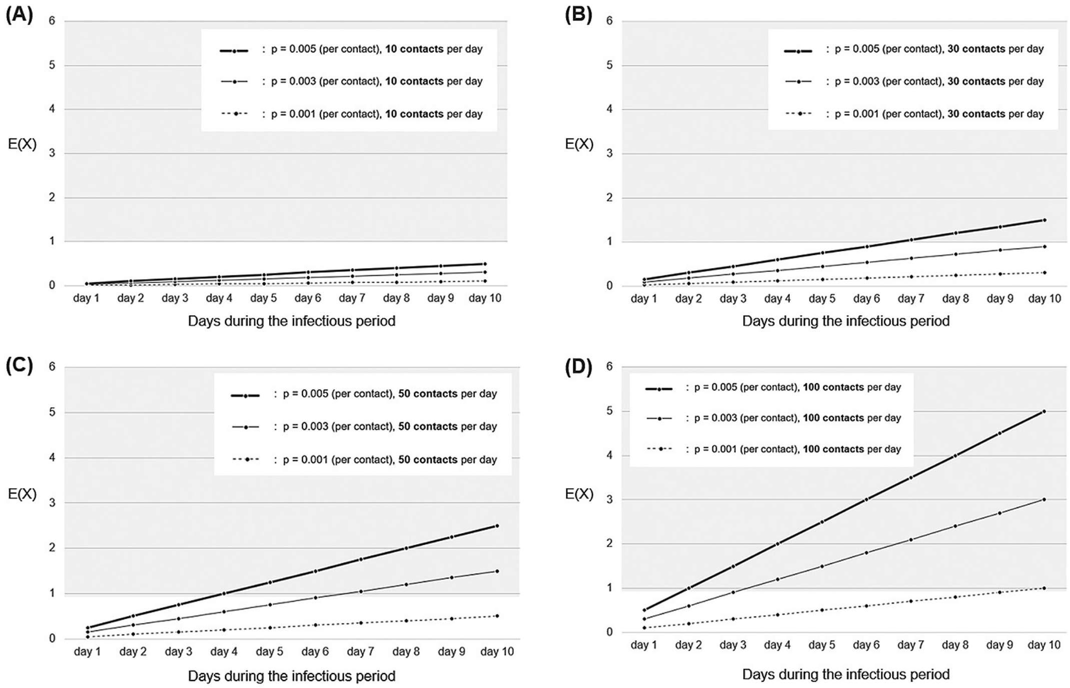

Fig. 4. Simulation of the COVID-19 spread at schools with different contact frequencies and transmissibility.
The line graphs show the cumulative expected numbers of secondary transmissions at schools during the infectious period of the index case. Conditions with different daily contact frequency of 10 (A), 30 (B), 50 (C), or 100 (D) contacts made by the index case per day at school and different transmissibility per contact (p = 0.001, 0.003, or 0.005) were applied. With the assumed secondary transmission rates at schools, early quarantine of the index cases and routine restriction of contact among students [i.e., ideally less than 30 (contacts/day)] during the pandemic would be helpful in preventing the spread of COVID-19 at schools.

rence of outbreak at schools.

A limitation of this study is that the applied models were those estimated from the current epidemic trends in the schools in Japan under the conditions of infection prevention measures announced by the Ministry of Education, Culture, Sports, Science and Technology, Japan (2020). Thus, the achieved value of the estimated secondary attack rate for each contact with 0.005 (i.e., 0.5%) may not be applicable to other countries with different lifestyles and different infection prevention measures (Larosa et al. 2020). Another limitation is that the present study was performed before the vaccination for Japanese citizens started in May 2021. Consequently, the estimated transmission rate and the derived results of the spread simulation in this study may be changed after the prevalence of vaccination among the children.

In conclusion, the present study estimated that the probability of secondary transmission after each contact at schools in Japan with current infection prevention measures would be approximately 0.5% per each contact. More than 30 contacts every day at school by the index case will make the expected value of secondary cases higher than 1.0 after the infectious period. Compliance with the current infection prevention measures at schools and early detection and quarantine of the index cases would be effective ways in preventing the outbreak occurrence at schools during pandemic.

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Conflict of Interest

The authors declare no conflict of interest.

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