Economic Evaluation of Wastewater Surveillance Combined with Clinical COVID-19 Screening Tests, Japan

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The COVID-19 pandemic has imposed substantial burdens on the global society. To find an optimal combination of wastewater surveillance and clinical testing for tracking COVID-19, we evaluated the economic efficiency of hypothetical screening options at a single facility in Japan. To conduct cost-benefit analyses, we developed standard decision models in which we assumed model parameters from literature and primary data, such as screening policies used at the Tokyo Olympic and Paralympic Village in 2021. We compared hypothetical 2-step screening options that used clinical PCR to diagnose COVID-19 after a positive result from primary screening using antigen tests (option 1) or wastewater surveillance (option 2). Our simulation results indicated that option 2 likely would be economically more justifiable than option 1, particularly at lower incidence levels. Our findings could help justify and promote the use of wastewater surveillance as a primary screening at a facility level for COVID-19 and other infectious diseases.

COVID-19, caused by SARS-CoV-2, has imposed substantial disease and social burdens on the global society; ≈6.85 million deaths were confirmed worldwide by February 2023 (*1*). To reduce disease burden, both clinical screening tests and epidemic surveillance systems are required and need to be efficiently implemented under tight budget constraints.

Although clinical PCR and antigen tests are essential for detecting individual cases, those tests have multiple limitations, such as testing avoidance behaviors, low detection rates among asymptomatic persons, and challenges when high demand for testing during epidemic peaks exceeds laboratory capacity. An additional limitation is the relatively high cost at a population level, which hinders frequent implementation even among high-risk subpopulations and essential workers. Because of those limitations, an epidemic surveillance system based on clinical tests tends to underestimate prevalence and have reduced representation because of insufficient sample sizes.

Wastewater surveillance is expected to address limitations of clinical tests (*2*). A sample of wastewater can be highly representative for all residents at a specific facility or for hundreds of thousands of residents in an area covered by a single wastewater treatment plant. Although wastewater surveillance is a risk measure of a community and not an individual resident, when compared as separate options, a simple cost comparison favors wastewater surveillance over clinical tests (*3*).

The appropriate sampling site can differ depending on the population level targeted by wastewater surveillance. When a large population is targeted, such as all residents within a citywide sewershed, sampling of influent wastewater at a wastewater treatment plant is most effective (*4*). When neighborhood-scale sewersheds are targeted, wastewater should be sampled from manholes or pumping stations (*5*). Finally, when a single facility is targeted, wastewater samples must be collected immediately after being discharged from the facility; in most cases, such samples can be collected from a manhole (*6*).

We aimed to find an optimal combination of wastewater surveillance and clinical testing that complement, rather than substitute for, each other. Therefore, we performed an economic evaluation to

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estimate the return on investment (ROI) of hypothetical screening options at a single facility in Japan.

Methods

We conducted a cost-benefit analysis to estimate the economic efficiency of various hypothetical screening options for confirming SARS-CoV-2 infections among asymptomatic or presymptomatic persons at a single residential facility, as measured by ROI, an equivalent to benefit-to-cost ratio. If 1 option is cost-saving compared with its comparator, that option's ROI is estimated to be >1. For example, an estimated ROI of 1.50 indicates that a $100 investment in 1 option will produce a net savings of $50. Our cost-benefit analyses adopted a societal perspective with a 1-month timeframe.

We compared 2 hypothetical 2-step screening options that used clinical PCR tests to diagnose individual COVID-19 cases after a positive result from a primary screening with antigen tests (option 1) or wastewater surveillance (option 2). Those screening options partly followed those used in the Tokyo Olympic and Paralympic Village in 2021 (*6*,*7*). We assumed antigen test results would be available in ≤1 hour, PCR test results would be available on the same day, and wastewater surveillance results would be available by the day after sampling.

More specifically, under option 1, the residents at a facility would all undergo antigen testing daily for 4 days as a primary screening. Any resident who tests positive would receive secondary screening on the same day with 2 PCR tests to confirm the diagnosis. Option 2 was to conduct wastewater surveillance at a facility as a primary screening for days 1–3. If a previous day's wastewater surveillance indicated a positive result, all persons at the facility would undergo secondary screening with 2 consecutive PCR tests to clinically diagnose an infected case during days 2–4.

Option 1 and option 2 are substitutes only in terms of their primary screening, either antigen tests or facility-based wastewater surveillance. For both options, the primary screening (antigen tests or facility-based wastewater surveillance) and secondary screening (PCR for clinical diagnosis) are complementary.

We assumed model parameters on the basis of available literature and primary data and developed a standard decision model (Table 1; Appendix Figure 1, https://wwwnc.cdc.gov/EID/article/29/8/22-1775-App1.pdf). Our base-case analysis with a deterministic model assumed a point estimate for each parameter. To address the uncertainties of model parameters, we also implemented a probabilistic analysis with Monte Carlo simulations by assigning distributions (Table 1). For instance, we assumed a triangular distribution for the parameter sensitivity of wastewater surveillance using a mode of 66% (range 46%–84%). That parameter sensitivity could be affected by various factors, including variability in viral shedding over the course of an infection and between different infected persons, dilution and decay of virus in the sewer, and analytical sensitivity of the method used for virus detection in wastewater. Monte Carlo simulations provided the mean and the 95% probabilistic confidence interval (PCI) values of the ROI estimates. We used TreeAge software (https://treeage.com) to perform analyses for decision models.

Because economic efficiency is highly sensitive to the disease incidence, our base-case analysis included the 3 scenarios: 10, 100, or 1,000 newly reported clinically positive cases per million residents per day (PMPD) in the area around the facility. In other words, our study did not assign a certain distribution for the incidence because of a very wide range of feasible values.

The 10 PMPD incidence value corresponds to the minimum level at which wastewater surveillance sampled at a wastewater treatment plant can detect SARS-CoV-2 (*4*). Our 1-way sensitivity analyses all assumed the incidence value of 100 PMPD, above which a correlation was observed in our primary data between SARS-CoV-2 RNA load in wastewater sampled at a wastewater treatment plant and the incidence based on clinical PCR tests in the area (*21*).

The 1,000 PMPD incidence value is equal to the ratio of 1 newly infected case among 1,000 residents in a hypothetical facility, and 1,000 was close to the smallest population of the sampling area in the Tokyo Olympic and Paralympic Village in 2021 (*6*). Our base-case analyses all assumed the facility had 100 residents, which we based on the average number of beds in long-term care facilities (LTCFs) in Japan (*22*).

Hypothetical study populations in our base-case analyses all were 100 residents at a LTCF who were expected to receive greater benefits from screening tests in terms of preventing COVID-19–related illness and death compared with the general population. For instance, LTCF residents in Japan have an average age of ≈86 years (*29*) and were estimated to be 19 times as likely to die after a clinical COVID-19 diagnosis than the general population in Japan (*23*).

Our study estimated the benefit of confirming 1 infected case by PCR under each screening option by using 2 components: the benefit of reducing hospitalization and death for a confirmed case, and

Table 1. Decision model parameters in an economic evaluation of wastewater surveillance combined with clinical COVID-19 screening tests, Japan*

Parameters†	Point estimate (range)	Reference
Test characteristics		
Sensitivity		
Wastewater surveillance	0.66 (0.46–0.84)	M. Kitajima, unpub. data
PCR‡	0.74 (0.64–0.83)	(*8*,*9*)
Ratio of antigen test against PCR test	0.76 (0.54–0.97)	(*8*–*10*)
PCR test after positive antigen test	0.99 (0.64–0.999)	(*8*,*9*)
Specificity		
PCR	0.974 (0.96–0.995)	(*9*,*10*)
Antigen test	0.99 (0.97–0.995)	(*10*)
Ratio of wastewater surveillance against PCR test	0.99	
Cost		
Laboratory cost of wastewater surveillance per facility per day	$379 ($189–$758)	(*11*,*12*)
Labor cost to sample at a facility per facility per day	$1,136 ($152–$2,045)	(*13*)
Antigen test§	$16 ($10–$23)	(*14*,*15*)
Clinical PCR§	$38 ($20–$53)	(*14*,*15*)
Isolation per test-positive case	$758 ($379–$1,515)	(*16*)
Hospitalization per case¶	$19,394 ($16,212–$25,227)	(*17*–*19*)
Value of QALY saved per case	$37,879	(*20*)
Other		
Incidence per day per 1 million residents	100 (10–10,000)	(*4*,*21*)
No. residents at a facility	100 (50–200)	(*6*,*22*)
Mortality rate among persons who test positive#	0.0035 (0.0018–0.0104)	(*23*)
Ratio of mortality rate among persons ≥80 years of age vs. general population	19 (15–22)	(*23*)
Life-years saved by avoiding COVID-19	11.4 (11.1–11.7)	(*24*,*25*)
Ratio to convert life-years saved to QALYs saved	0.68 (0.64–0.71)	(*24*,*26*)
Hospitalization rate among persons who test positive	0.18 (0.04–0.40)	(*17*)
Proportion of severe cases among hospitalized cases	0.1 (0.05–0.19)	(*17*)
Effective reproduction number of infected cases	1.3 (0.9–2.0)	(*27*)
Screening effectiveness in reducing hospitalization and mortality rates because of an earlier diagnosis	0.54 (0.23–0.62)	(*28*)
Ratio of loss value of missing an infected case compared with benefit value of finding an infected case	1 (0–2.0)	

*All monetary values are expressed in 2022 US dollars. QALY, quality-adjusted life-years.
†All parameters with a minimum and a maximum value in this table are defined as a triangular distribution in the probabilistic analysis, detailed in the Appendix (https://wwwnc.cdc.gov/EID/article/29/8/22-1775-App1.pdf).
‡Because the second clinical PCR test was conducted immediately after the first clinical PCR test, the sensitivity of the second clinical PCR was assumed to be equal to the specificity of the PCR test in this table.
§Test cost plus labor cost for sampling; 30 min multiplied by minimum wage of $7 USD per hour (*15*).
¶Hospitalization cost was assumed as $16,212 + $64,394 x (proportion of severe cases among hospitalized cases – 0.05).
#The range was defined to range from the rate before the vaccination period to the rate after the vaccination period (Appendix).

the benefit of preventing secondary infection. Because scant literature addressed the effectiveness of screening in reducing hospitalization and mortality rates among persons who test positive, we assumed effectiveness was equivalent to the clinical efficacy of antiviral agents among patients with COVID-19 at its early stage (e.g., ≤7 days after the onset of signs or symptoms), who are not hospitalized yet but could be subsequently hospitalized or die (*28*). We reduced the clinical efficacy by 30%, because 30% of infected persons never develop symptoms (*30*). Consequently, our screening effectiveness had a triangular distribution with a mode of 0.54 (range 0.23–0.62). We estimated the benefit of preventing secondary infection to be 0.57 under our base-case analyses, which was dependent on a reproduction number of 1.3 (*27*), an infectious period of 8.03 days (*31*), and other factors (*30*). In addition, our model accounted for the loss of missing an infected case that produced a second-generation infected case every day (Appendix).

To assign benefit values for reducing hospitalization and mortality rates, we estimated the related monetary value for 3 outcomes among confirmed cases: isolation (*14*–*16*), hospitalization (*17*–*19*), and death (*20*,*24*–*26*). All monetary values are expressed in 2022 US dollars (USD). We assigned a value for death by applying the monetary value of $37,879 for each quality-adjusted life-year (QALY) saved or lost under the cost-effectiveness analysis set by the Ministry of Health, Labour and Welfare of Japan (*20*). To estimate QALYs lost due to COVID-19, we first calculated life years lost based on age at death (*24*) and life expectancy among a certain age and sex (*25*). To convert life years lost to QALYs lost, we applied the ratios estimated among the population of the Netherlands (*26*), because the relevant data were not available for Japan.

Results

When COVID-19 incidence was 10 PMPD, our deterministic base-case analysis indicated that option 1 alone, compared with doing nothing (comparator do-nothing), was not economically justifiable because its cost ($67.04) exceeded its benefit ($1.39) and the ROI of 0.021 ($1.39/$67.04) was ≤1.0 (Table 2). Although option 2 alone compared with do-nothing was not justifiable because of the low ROI (0.021), option 2 became justifiable when its comparator was changed from do-nothing to option 1. That is, compared with option 1, option 2 saved $13.44, which could be interpreted as relative benefit, and had a $0.25 lower benefit, which could be interpreted as relative cost. Thus, compared with option 1, the relative value of option 2 was a high ROI of 54 ($13.44/$0.25) (Table 2).

When COVID-19 incidence was 1,000 PMPD under our base-case analysis, we estimated the ROI of option 1 to be 2.10 and of option 2 to be 2.23 (Table 2). One-way sensitivity analysis of the deterministic model showed the threshold incidence values, above or below which an option's ROI is >1. Those threshold values were 480 PMPD for option 1 alone, 450 PMPD for option 2 alone, and 630 PMPD for the relative value of option 2 (Table 3). One-way sensitivity analysis also showed that when incidence increased, the ROI of options 1 and 2 increased and that the relative value of option 2 declined (Figure).

Additional 1-way sensitivity analyses of the base-case analysis showed that within the feasible range of parameters, all 3 types of ROI estimates were sensitive to incidence and had values above and below 1.0. The ROI estimates of options 1 and 2 alone, compared with do-nothing, were robust to all parameters except incidence. The ROI estimates of options 1 and 2 alone had a negative association with test costs and a positive association with test sensitivity and specificity (Table 4).

The estimated range of the ROI for the relative value of option 2 includes negative values (Table 4). For the ratio of sensitivity of antigen tests against PCR, option 2 was always preferred over option 1; option 2 dominated option 1 when the ROI estimates were negative for that ratio. In other words, a simple linear relationship did not occur between the ratio of sensitivity of antigen tests against PCR and the ROI for the relative value of option 2. For instance, when that ratio increased from 0.64 to 0.97, the ROI estimate for the relative value of option 2 was always >1 (Appendix Table 8). When the ratio was 0.638, option 2's benefit became equal to option 1's benefit, which did not mathematically enable estimation of the ROI for the relative value of option 2. When the ratio increased from 0.54 to 0.63, option 2's benefit exceeded option 1's benefit; thus, option 2 dominated option 1.

The ROI estimates regarding the relative value of option 2 were sensitive to 3 cost-related parameters. In other words, an estimated threshold point existed, below or above which a preferred option changed. For instance, option 2 was preferred only when the labor cost to sample a facility was lower than the threshold point of $1,512. When labor cost exceeded that threshold point, option 1 was preferred. Likewise, when the cost of the antigen test was lower than the threshold point of $13.18, option 1 was preferred, but when it was greater than that threshold point, option 2 was preferred. Because the cost of wastewater surveillance per facility was fixed, the cost per facility resident could be substantially reduced by a larger number of facility residents. Therefore, when the number of residents was lower than the threshold point of 81, option 1 was preferred, but when it was greater than that threshold, option 2 was preferred.

The probabilistic analyses showed that the base-case analyses with a deterministic model were robust, particularly for cost, benefit, and ROI estimates for option 1 alone or option 2 alone (Table 5). Although the estimated PCIs included a large negative value as a lower bound, option 2 was mostly preferred to option 1 when the incidence was 10 or 100

Table 2. Base-case analysis with a deterministic model in an economic evaluation of wastewater surveillance combined with clinical COVID-19 screening tests, Japan*

	Option 1			Option 2			Relative value of option 2		
Incidence†	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Incremental cost§	Incremental benefit¶	Relative ROI#
10	$67.04	$1.39	0.021	$53.60	$1.14	0.021	–$13.44	–$0.25	54
100	$67.05	$14.09	0.21	$53.61	$11.94	0.22	–$13.43	–$2.15	6.25
1,000	$67.12	$141.11	2.10	$53.75	$119.94	2.23	–$13.37	–$21.16	0.63

*Option 1 is clinical testing only; option 2 is wastewater surveillance and clinical testing. If one option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing. All monetary values are expressed in 2022 US dollars (USD). ROI, return on investment.

†Disease incidence per day per 1 million residents in the area.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Table 3. One-way sensitivity analyses of the base-case analysis of the incidence parameter in an economic evaluation of wastewater surveillance combined with clinical COVID-19 screening tests, Japan*

	Option 1			Option 2			Relative value of option 2		
Incidence†	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Incremental cost§	Incremental benefit¶	Relative ROI#
10	$67.04	$1.39	0.02	$53.60	$1.14	0.02	–$13.44	–$0.25	54
50	$67.04	$7.03	0.10	$53.61	$5.94	0.11	–$13.44	–$1.09	12
100	$67.05	$14.09	0.21	$53.61	$11.94	0.22	–$13.43	–$2.15	6
400	$67.07	$56.43	0.84	$53.66	$47.94	0.89	–$13.41	–$8.49	1.58
445	$67.08	$62.78	0.94	$53.67	$53.34	0.99	–$13.41	–$9.44	1.42
450	$67.08	$63.49	0.95	$53.67	$53.94	1.01	–$13.41	–$9.54	1.40
475	$67.08	$67.01	0.999	$53.67	$56.94	1.06	–$13.41	–$10.07	1.33
480	$67.08	$67.72	1.010	$53.67	$57.54	1.07	–$13.41	–$10.18	1.32
500	$67.08	$70.54	1.05	$53.68	$59.94	1.12	–$13.40	–$10.60	1.26
600	$67.09	$84.65	1.26	$53.69	$71.94	1.34	–$13.40	–$12.71	1.05
630	$67.09	$88.89	1.32	$53.70	$75.54	1.41	–$13.39	–$13.35	1.004
635	$67.09	$89.59	1.34	$53.70	$76.14	1.42	–$13.39	–$13.45	0.996
700	$67.10	$98.77	1.47	$53.71	$83.94	1.56	–$13.39	–$14.83	0.90
1,000	$67.12	$141.11	2	$53.75	$119.94	2	–$13.37	–$21.16	0.63
2,000	$67.20	$282.23	4	$53.91	$239.95	4	–$13.29	–$42.29	0.31
5,000	$67.45	$705.62	10	$54.37	$599.96	11	–$13.07	–$105.66	0.12
10,000	$67.85	$1,411.26	21	$55.14	$1,199.97	22	–$12.71	–$211.29	0.06

*Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing. All monetary values were expressed in 2022 US dollars. ROI, return on investment.

†Disease incidence per day per 1 million residents in the area.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

PMPD. More specifically, over 1,000 iterations, when incidence was 10 PMPD, option 2 was preferred in 84.7% of the time; when incidence was 100 PMPD, option 2 was preferred 80.8% of the time; and when incidence was 1,000 PMPD, option 2 was preferred 25.2% of the time. Thus, qualitative conclusions of probabilistic analyses were similar to those of deterministic analyses.

Discussion

Our simulation results indicate that a primary screening with wastewater surveillance (option 2) at a single facility was highly likely to be economically more justifiable than a primary screening with antigen tests (option 1), particularly at lower incidence levels (<630 PMPD). Option 2 tended to have a much lower cost (interpreted as relative benefit) and a slightly lower benefit (interpreted as relative cost) compared with option 1. Of note, when the comparator was do-nothing, option 1 alone and option 2 alone had low economic efficiency when the disease incidence was low; option 1 alone was economically justifiable only when the incidence was >480 PMPD and option 2 alone was economically justifiable only when the incidence was >450 PMPD. At incidence levels >1,000 PMPD, option 2 is economically less efficient than option 1 because clinical tests would not be implemented on day 1 under option 2, which would lead to more secondary infections and more costs for isolation or hospitalization. Our results appeared generally robust to the feasible range of model parameters, although some results were sensitive to parameters related to the disease incidence and cost of tests.

Our analytical models are expected to have high generalizability to and be robust for SARS-CoV-2 variants, unlike vaccination effectiveness, which can potentially be reduced by variants. In addition, our analytic approach would be readily applicable to other emerging infectious diseases.

The negative ROI estimates regarding the relative value of option 2 should be interpreted with caution because 2 opposite interpretations are possible. One interpretation prefers option 2, such as when option 2 detected many more infected cases than option 1 at a facility with <77 residents. On the contrary, the other interpretation prefers option 1, such as when fewer COVID-19 cases were missed by option 1 than option 2 and when the antigen test cost was <$12.64.

We expected the face validity of our simulation results to be achieved to some extent, partly because the assumptions of our hypothetical screening options mainly followed the screening policies used in the Tokyo Olympic and Paralympic Village (*6*,*7*). Also, the assumed range of the laboratory cost for wastewater surveillance ($189–$758) appeared reasonable, compared with costs reported by other studies (*11*,*12*,*32*).

In addition, we used conservative assumptions in our base-case analysis, such as relatively high costs for additional labor to sample wastewater at a facility for surveillance (*13*). Another set of conservative assumptions that reduced the benefit of confirming 1 infected case were the exclusion of COVID-19–related medical expenditure for outpatient care and the possible financial loss related to shutdown of a LTCF. We excluded those items from our analyses because cost-related data were absent in the literature.

One weakness of this study is the limited generalizability to other settings. We assumed the monetary value of finding 1 COVID-19 case at a facility depended partly on related medical expenditure and QALY saved. QALY varies in different countries; in Japan, the value is $37,879/QALY (*20*). Also, the monetary value of finding 1 case consisted of mortality rate in the population, hospitalization rate in the population, and medical expenditures per hospitalized case, all of which could vary substantially at the population level because of viral variants occurring over time and across regions within a country. In addition, mortality and hospitalization rates vary markedly among subpopulations defined by age and high-risk chronic conditions. Such uncertainties indicate the need to frequently update the simulation model to correspond to regional epidemics and target populations.

Because of the absence of literature, the validity of our ROI estimates was difficult to compare with estimates from previous studies. Although 1 study compared wastewater surveillance at a treatment plant and clinical PCR tests in its costs, that study compared cost per population screened without accounting for clinically confirmed cases after wastewater surveillance (*3*). Therefore, the estimates in that study were not appropriate comparisons for our ROI estimates. When the goal of screening is to identify and isolate an infected case, wastewater surveillance should be used as a primary screening, after which secondary screening should be performed by using clinical tests.

Major policy implications derived from this study's findings are exemplified by the threshold levels to start or suspend a specific screening option. Compared with do-nothing, threshold incidence levels were 480 PMPD for option 1 alone and 450 PMPD for option 2 alone, but those thresholds are <1,000 PMPD. The 1,000 PMPD incidence is equivalent to 1 newly infected case at a single large facility with 1,000 residents. That is, before finding the first newly infected case at a single facility, options 1 and 2 should be started, ideally triggered when the incidence of the area around the facility, such as the city, town, or neighborhood, reaches the threshold levels we reported for each option.

The ROI estimates for the relative value of option 2 compared with option 1 tended to be high at a very low incidence, when the absolute benefit of option 2 is small compared with do-nothing. One practical incidence level to trigger option 2 is 10 PMPD, above which wastewater surveillance conducted by using a recently developed method can detect SARS-CoV-2 RNA at a treatment plant (*4*). Another trigger incidence is 100 PMPD, above which conventional wastewater surveillance methods can detect SARS-CoV-2 RNA (*4*). Regularly monitoring data from wastewater surveillance at a treatment plant could enable efficient triggers for option 1 and option 2 at a specific facility in the same area.

Because wastewater surveillance at a treatment plant covers a city-scale population, the additional cost per resident would be very small, even when

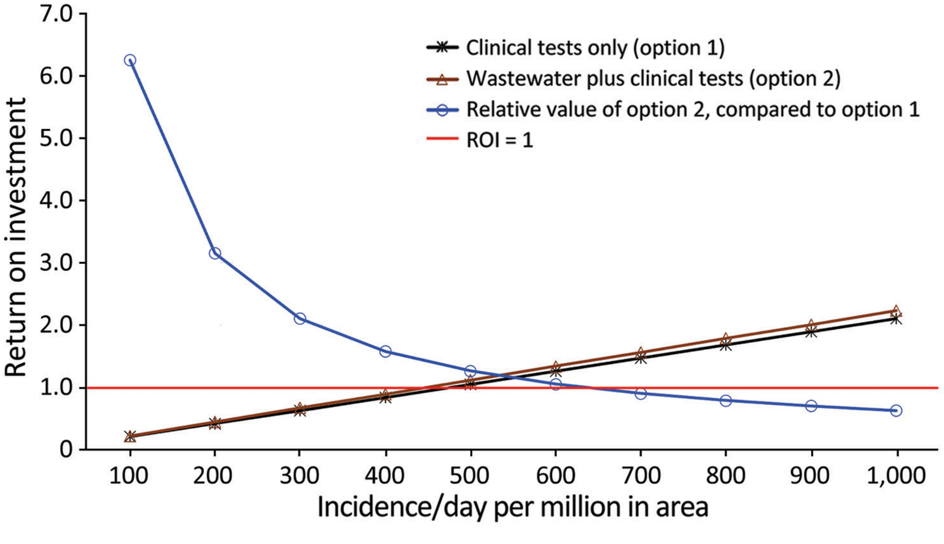

Figure. ROI comparison of 2 options used in an economic evaluation of wastewater surveillance combined with clinical COVID-19 screening tests, Japan. ROIs for the relative value of option 2 are expressed as $\log_{10}$ and determined by 1-way sensitivity analyses of the base-case analysis (Table 3). Red horizontal line indicates ROI = 1. ROI, return on investment.

focusing on an institutionalized population; for instance, increasing the per resident cost in our model by <1%. Although the central government of Japan implemented pilot projects of wastewater surveillance at both city and facility levels during fiscal year 2022 (33), government officials did not expand the scale of those projects, partly because of a lack of evidence regarding economic efficiency. Thus, our findings could help the central government of Japan justify the expansion of these projects.

Table 4. One-way sensitivity analyses of the base-case analysis in an economic evaluation of wastewater surveillance combined with clinical COVID-19 screening tests, Japan*

Parameters	Parameter values	Return on investment†		Relative ROI‡
		Option 1	Option 2	
Test characteristics				
Sensitivity				
Wastewater surveillance	0.46	0.21	0.12	2
	0.84	0.21	0.26	80
PCR	0.64	0.18	0.22	32
	0.83	0.23	0.22	4
Ratio of antigen test against PCR test	0.54	0.14	0.22	−5.43
	0.97	0.24	0.22	3
PCR test after positive antigen test	0.64	0.12	0.10	5
	0.999	0.21	0.22	6
Specificity				
PCR	0.96	0.21	0.21	5
	0.995	0.21	0.25	9
Antigen test	0.97	0.19	0.22	9
	0.995	0.22	0.22	6
Cost				
Wastewater surveillance cost per day per facility				
Laboratory cost	$189	0.21	0.25	9
	$758	0.21	0.18	0.96
Labor cost to sample	$152	0.21	0.50	20
	$2,045	0.21	0.15	−6.43
Antigen test¶	$10	0.33	0.22	−4.91
	$23	0.15	0.22	19
Clinical PCR¶	$20	0.215	0.24	7
	$53	0.207	0.21	5
Isolation per test-positive case	$379	0.209	0.222	6.33
	$1,515	0.212	0.224	6.09
Hospitalization per case#	$16,212	0.18	0.19	7
	$25,227	0.26	0.27	5
Other				
Incidence per day per 1 million population	10	0.02	0.02	54
	10,000	21	22	0.06
No. residents at a facility	50	0.21	0.12	−14.89
	1,000	0.21	0.94	25
Mortality rate among persons who test positive	0.0018	0.19	0.20	7
	0.0104	0.30	0.32	4
Ratio of mortality rate among persons ≥80 years of age vs. the general population	0.5	0.004	0.004	161
	22	0.24	0.26	5
Life-years saved by avoiding COVID-19	11.1	0.209	0.221	6.28
	11.7	0.211	0.224	6.21
Ratio to convert life-years saved to QALYs saved	0.64	0.207	0.220	6.33
	0.71	0.212	0.225	6.19
Hospitalization rate among persons who test positive	0.04	0.08	0.08	14
	0.40	0.42	0.46	4
Proportion of severe cases among hospitalized cases	0.05	0.18	0.19	7
	0.19	0.26	0.28	5
Effective reproduction number of infected cases	0.9	0.28	0.31	7
	2.0	0.17	0.16	5
Effectiveness of screening in reducing hospitalization and mortality rates because of an earlier diagnosis	0.23	0.09	0.10	14
	0.62	0.24	0.26	5
Ratio of loss value of missing and infected cases compared with benefit value of finding an infected case	0.0	0.25	0.31	148
	2.0	0.17	0.13	3

*The lower and upper bounds of each parameter are shown to illustration the association between a parameter and its ROI. Incidence was assumed to be 100 persons per day per 1 million residents in the area. All monetary values are expressed in 2022 US dollars. QALY, quality-adjusted life-years; ROI, return on investment.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests.

‡Relative ROI of option 2 compared with option 1.

Table 5. Base-case analysis using a deterministic model and a probabilistic model in an economic evaluation of wastewater surveillance combined with clinical COVID-19 screening tests, Japan*

	Option 1			Option 2			Relative value of option 2		
Incidence†	Cost	Benefit	ROI 1‡	Cost	Benefit	ROI 2‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
10									
DA	$67.04	$1.39	0.021	$53.60	$1.14	0.021	–$13.44	–$0.25	54
Mean PA	$70.03	$1.43	0.021	$50.68	$0.97	0.021	–$19.35	–$0.46	45
(95% PCI)	($49.85–$90.25)	($0.42–$2.85)	(0.006–0.043)	($25.27–$90.23)	($0.19–$2.04)	(0.004–0.051)	(–$54.48 to $24.31)	(–$1.20 to $0.08)	(−194 to 387)
100									
DA	$67.05	$14.09	0.21	$53.61	$11.94	0.22	–$13.43	–$2.15	6.25
Mean PA	$68.54	$14.75	0.22	$50.86	$10.37	0.23	–$17.68	–$4.38	5.74
(95% PCI)	($48.77–$88.86)	($5.11–$28.35)	(0.07–0.45)	($24.95–$92.14)	($3.03–$20.71)	(0.05–0.60)	(–$52.33 to $23.34)	(–$11.35 to $1.31)	(−24 to 37)
1,000									
DA	$67.12	$141.11	2.10	$53.75	$119.94	2.23	–$13.37	–$21.16	0.63
Mean PA	$69.50	$147.29	2.17	$50.61	$104.58	2.29	–$18.89	–$42.71	0.34
(95% PCI)	($48.76–$89.54)	($52.37–$279.00)	(0.73–4.57)	($24.56–$89.89)	($30.91–$215.00)	(0.55–5.59)	(–$52.28 to $23.15)	(–$110 to $8.65)	(−2.14 to 3.71)

*A probabilistic model to compare clinical tests only (option 1) to wastewater surveillance combined with clinical tests (option 2). If one option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing. DA, deterministic model analysis; inc., incremental; PA, probabilistic model analysis with Monte Carlo simulations; PCI, probabilistic confidence interval; rel., relative; ROI, return on investment.

†Disease incidence per day per 1 million residents in the area.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Another major policy implication is the threshold level for the number of residents at a facility. Our base-case analyses used hypothetical study populations of 100 residents at an LTCF. Our sensitivity analyses showed that the ROIs for option 2 alone and relative value of option 2 might increase when the number of residents increased; hence, wastewater surveillance cost per resident declined. The number of residents per facility could be easily increased to >1,000, the upper bound of our 1-way sensitivity analyses, if a facility, such as a large apartment complex, included younger residents. However, a lower mortality rate for younger residents would reduce the general screening benefit, thus reducing the ROI. An estimated minimum (threshold) number of 81 residents at an LTCF appears to help set a public guideline for wastewater surveillance.

Additional policy implications would help set goals for related industry. Because option 1 and option 2 differ in a primary screening, the difference in sensitivity between antigen tests and wastewater surveillance affected the economic efficiency for the relative value of option 2. Improved sensitivity of antigen tests is feasible but requires a longer time to diagnose a case, which reduces the benefit of antigen tests by postponing the diagnosis timing compared with 1-hour diagnosis time assumed under our base-case analysis. In other words, shortening the time to diagnosis for a screening test result would generally improve the test's economic efficiency, a goal for related industry.

Future research could further explore the monetary values of time needed for screening, such as time required by caregivers who collect samples from LTC residents or young children. If those time costs are much larger in a certain setting, like a kindergarten, the relative economic efficiency of wastewater surveillance against clinical tests would increase.

Although one of the general advantages of wastewater surveillance is fewer privacy and stigmatization concerns than possible with clinical surveillance (*34*), ethical issues could arise in 2 cases. First, targeting a specific facility or a small catchment could lead to social harm and financial burdens to the targeted population (*34*). Second, regardless of the target population size, ethical issues might arise when the wastewater surveillance is used for applying restrictive measures, such as group quarantine or business closure in the target area or facility (*35*). Researchers, policymakers, and regulators need to collaborate to account for ethical issues in implementing wastewater surveillance (*36*), which could enable wastewater surveillance to represent a new frontier in surveillance, monitoring, and screening.

In conclusion, our findings could help justify and promote the use of wastewater surveillance as a primary screening at a single facility when a set of quantified conditions estimated in our simulation are met.

Of note, regular wastewater surveillance at a treatment plant will help trigger the start of any screening tests at a specific facility. Because few economic evaluations of wastewater surveillance have yet been conducted, our findings can contribute to related academic fields and policy making.

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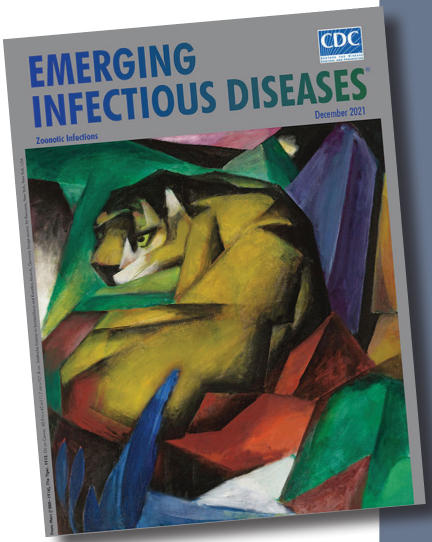

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etymologia revisited

Trichinella spiralis

[tri kuh neh′ luh spr a′ luhs]

Trichinella is derived from the Greek words *trichos* (hair) and *ella* (diminutive); *spiralis* means spiral. In 1835, Richard Owen (1804–1892) and James Paget (1814–1899) described a spiral worm (*Trichina spiralis*)–lined sandy diaphragm of a cadaver. In 1895, Alcide Raillet (1852–1930) renamed it as *Trichinella spiralis* because *Trichina* was attributed to an insect in 1830. In 1859, Rudolf Virchow (1821–1902) described the life cycle. The genus includes many distinct species, several genotypes, and encapsulated and nonencapsulated clades based on the presence/absence of a collagen capsule.

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Economic Evaluation of Wastewater Surveillance Combined with Clinical COVID-19 Screening Tests, Japan

Appendix

Supplementary Methods

This supplemental section explains the details of the methods, mainly the parameters in this study's decision models. Appendix Figure 1 shows the possible scenarios for a hypothetical facility resident. Our base case analyses with a deterministic model assumed the point estimate for each parameter in Table 1.

Test Characteristics: Sensitivity and Specificity

Since PCR tests' sensitivity depends on the sampling procedures, our clinical PCR tests' sensitivity parameter was assumed to consist of two components. The first component is the sensitivity of clinical PCR tests using nasopharyngeal swabs as the standard, which was assumed to follow a triangular distribution with a mode of 89%, varying from 85.4%–91.8%, based on a systematic review (*1*).

The second component is a ratio that captures the sensitivity's uncertainties depending on sampling procedures, compared to the standard of nasopharyngeal swabs. Another systematic review estimated this ratio as follows: pooled nasal and throat swabs (97%), saliva swabs (85%), nasal swabs (86%) and throat swabs (68%) (*2*). Based on these estimates, the second component ratio was assumed to follow a triangular distribution with a mode of 86% (i.e., a median of the four estimates above), ranging from 68%–97%.

We conducted a Monte Carlo simulation using these two components' distributions with 1,000 iterations, to obtain the mean (74%) with the 95% probabilistic confidence interval (PCI) of 64%–83%. Using these three estimates, our parameter on the sensitivity of clinical PCR tests (parameter name of sns_PCR in the decision tree) was assumed to follow a triangular distribution with a mode of 74%, varying from 64%–83%. The mode value of 74% was assumed to be a point estimate in a deterministic model.

Our study's antigen test is assumed to use rapid methods. Hence, results of an antigen test are assumed to be available within one hour after sampling. This rapid methods' sensitivity was estimated to be 72% by a systematic review study (*3*). This review study also estimated antigen tests' sensitivity to range from 40%–72%, depending on sampling procedures, e.g., nasopharyngeal samples or throat saliva samples (*3*). Using these estimates, our study assumed antigen tests' sensitivity to range from 40%–72% with a point estimate of 56%, which is the midpoint of this range.

Within one facility, the sensitivity of a primary screening with antigen tests was assumed to be lower than that of a secondary screening with clinical PCR tests. Thus, our study defined the antigen tests' sensitivity to consist of two components: the sensitivity of clinical PCR tests (described earlier) and the ratio of sensitivity of antigen test against clinical PCR tests that is <1. The latter ratio component (sns_Ag_ratio_PCR) was assumed to follow a triangular distribution with a mode of 76% (i.e., 56%/74% in which antigen tests' point estimate stated in the previous paragraph/mode of the clinical PCR tests' sensitivity defined earlier), varying from 54%

(40%/74%, in which antigen tests' minimum value/mode of the clinical PCR tests' sensitivity) to 97% (72%/74% = antigen tests' maximum value/mode of the clinical PCR tests' sensitivity).

As assumed in the previous paragraph, the sensitivity of a primary screening with antigen tests was lower than that of a secondary screening with clinical PCR tests. Therefore, when an infected case has a positive result in an antigen test, this case is highly likely to have a positive result in subsequent clinical PCR tests, e.g., 0.99 as a mode of these clinical PCR tests' sensitivity (sns_PCR_2nd). This parameter was assumed to range from 0.64 (i.e., the lower bound of the clinical PCR test defined above) to 0.999.

Our parameter on the specificity of antigen tests was to assume to follow a triangular distribution with a mode of 99%, varying from 96%–99.5%. The mode value of 99% was the median value of the eighteen studies examined in a systematic review (*3*). The minimum and the maximum values of these eighteen studies were 96%–99.5% (*3*).

The parameter on the specificity of PCR tests was assumed to follow a triangular distribution with a mode of 97.4%, varying from 96%–99.5%. The mode value of 97.4% was the weighted average of four sampling procedures among populations including asymptomatic subpopulations reported in a systematic review study (*2*). The minimum value of these four sampling procedures was 96% (*2*), which was used as a lower bound of the triangular distribution. The maximum value of 99.5% was assumed to be equal to that of antigen tests (*3*).

Cost of Tests

We defined two cost parameters to operate wastewater surveillance at a facility with a common unit of per day per facility: the laboratory cost and the labor cost to sample at a facility. Our parameter on the laboratory cost was assumed to follow a triangular distribution with a mode of $379, varying from $189–$758 (50%–200% of the mode). We used the exchange rate of

¥132 per $1 USD based on the time-series statistics data (annual average exchange rate) by the Bank of Japan in 2022 (*4*).

The mode value ($379 USD) was based on a price set by a laboratory company in Japan, which was similar to the cost of $300 USD reported by Safford and colleagues (*5*). We assumed that this price by a Japanese company included both a depreciation cost of the laboratory equipment (also called a fixed cost as an economics term) and a per-sample cost of consumables of reagents (also called a variable cost). The former and the latter costs were reported as $100,000 USD and $25 USD, respectively, by Kantor and associates (*6*), who did not report the total number of samples to completely depreciate the equipment cost. If this total number of samples is 295, the appropriate per-sample cost is estimated by summing a variable cost ($25) and a part of fixed costs ($339 = $100,000/295), i.e., $364 USD, which is equivalent to the point estimate of our cost parameter reported in the previous paragraph.

The labor cost to sample at a facility increased substantially if an additional operation at a public road outside a facility site, e.g., opening a manhole along a public road, was needed. This additional operation inflated the cost from $152 to $2,045 (*7*), which corresponded to a minimum value and a maximum value, respectively, in a triangle distribution assumed for this labor cost parameter. This distribution's mode value of $1,136 was close to a midpoint of this range.

The above two cost parameters were constant per facility per day regardless of the number of residents at a facility. Therefore, the cost of operating wastewater surveillance per facility resident declines, if "the number of residents at a facility" increases. Hence, the parameter on "the number of residents at a facility" is among cost related parameters. This parameter was assumed to follow a triangular distribution with a mode of 100, ranging from 50–200. The mode value was close to the maximum value among the four major types of long-term care (LTC) facilities' average number of beds in Japan (*8*). The minimum value was close to the minimum value among these four types of LTC facilities (*8*). This distribution's maximum value of 200, assumed as 200% of the mode. Under a one-way sensitivity analysis of this parameter, the upper bound was 1,000, which was close to the smallest population size of a sampling area in the Tokyo Olympic and Paralympic Village in 2021 (*9*).

Our parameters for costs of clinical tests were defined based on the list of approved tests posted in the Japanese government website (*10*). Since the price information of these tests are limited, our parameters might be biased either upward or downward. In addition to the test cost, we assigned a labor cost to collect a test sample, which was calculated as the 30-minute time cost with the minimum wage ($7 USD per hour) in Japan, as explained in the footnote of Table 1 in the manuscript (*11*). Consequently, the parameter on antigen tests' cost was assumed to follow a triangular distribution with a mode of $16, varying from $10–$23. The parameter on clinical PCR tests' cost was assumed to follow a triangular distribution with a mode of $38, ranging from $20–$53.

Benefit of Confirming One Infected Case

Our study assumed the benefit of confirming one infected case by PCR tests under options 1 and 2, consisted of two components: the benefit of reducing hospitalization and mortality rates among the confirmed case and the benefit of preventing secondary infection. The former component is explained in this subsection.

Benefit of Reducing Hospitalization and Mortality Rates among Confirmed Cases

There is little literature that quantified the screening effectiveness in reducing hospitalization and mortality rates among a screened population. Thus, we assumed this effectiveness to follow the clinical efficacy of antiviral agents among non-hospitalized patients with COVID-19. A systematic review based on a meta-analysis reported that this clinical efficacy was 77% in terms of lowering the risk of COVID-19–related hospitalization or death among cases within seven (or five) days after the onset of signs or symptoms (*12*). This review paper also estimated the efficacy for each of three types of antiviral agents, ranging from 33%–88% (*12*). In our study, these estimates were reduced by 30%, since 30% of infected individuals never develop symptoms (*13*). Consequently, our screening effectiveness was assumed to follow a triangular distribution with a mode of 0.54 (77% × [100%–30%]), ranging from 0.23 (33% × [100%–30%]) to 0.62 (88% × [100%–30%]) (Eff_early_Dx in Decision model). Our sensitivity analyses showed the robustness of our results regarding this parameter.

To assign benefit values for reducing hospitalization and mortality rates, we estimated the related monetary value for the three outcomes of isolation, hospitalization, and death among individuals confirmed as test positive. All individuals were assumed to be either isolated or hospitalized before a death. The hospitalization rate among test positives was assumed to follow a triangular distribution with a mode of 0.18, varying from 0.04–0.40 ("r_hosp_test_positive" in Decision model). Thus, under a base case analysis, 18% (the distribution mode was equal to a point estimate) and 82% (100% – 18%) among test-positives were hospitalized and isolated, respectively.

This distribution's mode value (0.18) was equal to the mean of the hospitalization rates among test-positives during a period from June 2, 2021–August 3, 2022 (*14*). The maximum value of 0.40 was equal to the average of the four hospitalization rates reported weekly from December 1–22, 2021 (i.e., as of December 1, 8, 15, and 22, 2021), when the epidemic level was very low and hence access to hospital care was guaranteed (*14*). The minimum value of 0.04 was equal to the average of the four rates reported weekly from June 1–22, 2022 (i.e., as of June 1, 8, 15, and 22, 2022), when the epidemic level was very high and hence access to hospital care was limited (*14*).

Isolation Related Cost

The isolation related cost included two cost items. The first cost item covers an isolation room with meals during the isolation period. The second item covers two additional PCR tests to end an isolation period. The first cost item was assumed to follow a triangular distribution with a mode of $758, ranging from $379–$1,515 (C_isolation in Decision model), based on the specific fee schedule set by the Japanese government (*15*).

Hospitalization Cost

Among hospitalized cases, three severity levels were assumed to follow the Japanese government fee-for-service (FFS)–based payment rates (*16*). The proportion of most severe cases was estimated to have a mean of 10%, varying from 5%–19%, based on the weekly variations during a period from June 2, 2021–August 3, 2022 (*14*). Using these estimates, the proportion of severe cases among hospitalized cases was assumed to follow a triangular distribution with a mode of 0.1, varying from 0.05–0.19 ("r_icu_hosp" in Decision model).

Among non-severe cases, the percentage of the light cases were estimated to be 64% and moderate cases were estimated to be 36% based on the publicly available data in Japan (*16*). Thus, the proportions of three severity levels were estimated (Appendix Table 1). For instance, when the proportion of severe cases was 10% (at its mode), the remaining proportions of light were estimated to be 58% and moderate cases were estimated to be 32%.

To estimate a total cost for a hospitalized case, a supplemental payment rate should be added to the FFS–based payment rate (Appendix Table 2). There is a marked difference between these two payment rates. That is, the FFS–based payment rate was applied only for an actual admission. On the other hand, a supplemental payment rate is paid for a hospital that secured a hospital bed for "potential" COVID-19 admissions, even if this bed is not occupied (*17*). Since our analysis adopted the societal viewpoint, the payments made for unoccupied beds should be assigned for admitted patients. For instance, if the bed occupancy rate is 50%, the average payment rates per an actual admission should be inflated twice (i.e., 100% ÷ 50%). The observed occupancy rate was variable, e.g., <10% for a certain period, which seemed difficult to assign a reasonable distribution. To make the most conservative estimates, the values in the column of "Supplemental payment rate per day per case" in Appendix Table 2 assumed the bed occupancy rate of 100%. Our conservative estimates are likely to underestimate the total hospitalization costs.

For each of three columns in Appendix Table 1, the weighted average of the total hospitalization cost was estimated. For instance, when the proportion of severe cases was 10%, the weighted total hospitalization cost was around $19,384 ($10,322 × 58% + $17,731 × 32% + $77,229 × 10%; weighting severity-specific costs listed in the far-right column of Appendix Table 2). Likewise, when the proportions of severe cases were 5% the total hospitalization cost estimates were ≈$16,212 and at 19% were ≈$25,227. Using these three estimates, a linear association was assumed between "the proportion of severe cases (r_icu_hosp)" and "total hospitalization cost (C_hosp_all)," mathematically expressed below:

$$(\text{C\_hosp\_all}) = \$16{,}212 + \$64{,}394 \times (\text{r\_icu\_hosp} - 0.05)$$

Death Related Value

We assigned monetary values for deaths due to COVID-19 by applying the monetary value ($37,879) for a quality adjusted life year (QALY) saved or lost under the cost-effectiveness analysis set by Japan's Ministry of Health, Labor and Welfare (*18*). To estimate

QALYs lost due to COVID-19, we first calculated life years lost based on “age at death” (*19*) Appendix Tables 3, and “life expectancy among a certain age and gender group,” (*20*) Appendix Tables 4, where age groups were classified into 10 groups, e.g., “<10 years old,” “10–19,” and “≥90.”

Since we used sex-specific life expectancies from Appendix Table 4, we disregarded the data in the third and far right columns in Appendix Table 3 where sex was not disclosed. For simplicity, we assumed that the average age of each age category in Appendix Table 3 is a mid-point, e.g., age 15 for the age group of “10–19.” As an exception, the average for the oldest age group of “≥90” in Appendix Table 3 was assumed to be 90, since the life expectancy value is not available for age ≥ 90 years in the sources of Appendix Table 4 (*20*).

The life years lost among the group of “male and age at 10s (average age of 15)” was equal to “66.89 (2nd row, 1st column in Appendix Table 4).” Applying this calculation for all sex-age groups in Appendix Table 3 (left columns of data up to December 27, 2021, when the “5th wave” ended in Japan), the average lost life years (weighted by the age-sex distribution) was estimated to be 11.7 years (not presented in tables). Using other death data in this table (left columns of data up to August 1, 2022, most recent data analyzed), this estimate was 11.1 years. Using these two estimates, the parameter on life years saved (V_life_yrs_saved in Decision model) was assumed to follow a triangular distribution, ranging from 11.1–11.7, with a mode of 11.4 (the average of these two estimates).

To convert “life years lost” to “QALYs lost,” we applied the ratios among the Dutch population (*21*), due to the absence of relevant data in Japan. Wouterse and associates estimated that the sex-specific ratios were 0.71 (men) and 0.64 (women) (*21*). Using these two estimates, the parameter on the ratio to convert “life years lost” to “QALYs lost” (r_QALY_adj in Decision model) was assumed to follow a triangular range from 0.64–0.71, with a mode of 0.68. This mode value was the weighted average of these two estimates, where weights were the sex proportions among cumulative COVID-19 deaths (up to August 1, 2022) in Japan, i.e., 0.584 (men) and 0.416 (women) (*19*).

Since our interest is to measure the benefit of confirming test positive cases by a screening, we estimated "the mortality rates among test positives" for each of the general population and the subpopulation $\geq$80 years of age. The latter age group was selected because average age of LTC facility residents was around 86 in Japan (*22*). The COVID-19 mortality rates could vary due to a population vaccination rate and viral variants unique to each epidemic wave. Thus, we estimated the mortality rates during the three periods: up to the 6th wave (September 8, 2020–May 31, 2022), up to the 5th wave (September 8, 2020–January 4, 2022), and during the 6th wave (January 4, 2022–May 31, 2022), excluding a period of the ongoing 7th wave as of August 25, 2022 (*23*) (Appendix Table 5).

Additionally, since the average hospital length of stay among severe cases was 21 days (*16*), the data period for deaths (numerator) was extended for 1–4 weeks (Appendix Table 5). Of note, age-specific mortality rates were available only after September 8, 2020 (*23*). Using the estimates in this table, the model parameter on the mortality rate among test positives (r_mortality_test_positive in Decision model) was assumed to follow a triangular distribution with a mode of 0.0035, ranging from 0.0018–0.0104 among the general population. The parameter concerning the ratio of mortality rate among persons $\geq$80 years of age, compared to the general population (V_mr_ratio) was assumed to follow a triangular distribution with a mode of 19, varying from 15–22, based on the estimates in this table (*23*).

Based on the parameters defined thus far, we estimated the monetary value of one confirmed case regarding the hospitalization and the mortality rates under a base case analysis among the general population, as mathematically expressed below.

Value of hospitalization for one confirmed case = Hospitalization rate × Hospitalization cost per admission, i.e., 18% × $19,384 per admission = $3,489

Value of mortality for one confirmed case = Mortality rate × Life years lost × Conversion to QALY × Value per QALY, i.e., 0.0035 × 11.4 × 0.68 × $37,879 = $1,028

Among the LTC residents, these values above will be inflated by 19, which assumes that the ratio of age-specific hospitalization rates was equal to that of mortality rates derived from the estimates in Appendix Table 5 (*23*). This is because there was no literature concerning the ratio of age-specific hospitalization rates in Japan.

Consequently, when the screening effectiveness in reducing hospitalization and mortality rates because of an earlier diagnosis (Eff_early_Dx) is assumed as 0.54 under our base case analysis, its benefit is expressed below.

Benefit of reducing hospitalization and mortality rate for a confirmed case = 0.54 × (values of hospitalization + value of mortality) × Ratio of mortality/hospitalization among persons $\geq$80 years of age = 0.54 × ($3,489 + $1,028) × 19 = $46,343

Benefit of Preventing Secondary Infection

As explained earlier, our study assumed the benefit of confirming one infected case by PCR tests under both option 1 and option 2, consisted of two components: the benefit of reducing hospitalization and mortality rates among the confirmed cases and the benefit of preventing secondary infection. The latter component is explained in this subsection.

Appendix Figure 2 shows our calculation method to quantify the number of secondary infected cases prevented by a confirmatory PCR test. Two key parameters are the reproduction number (R_e in this figure) on the figure's y-axis and the infectious period (e.g., 10 days (*13*) assumed in this figure) on the x-axis. Also, the number of preventable secondary infected cases depends on "screening timing during an infectious period (that cannot be observed)" and "time lag between screening timing and isolation timing."

The best-case scenario was indicated by a point in Appendix Figure 2, where the PCR sample was collected at the moment when an infectious period starts (i.e., 0 on the x-axis). Under this best-case scenario, the PCR result is available immediately and hence the infected case is isolated without producing any secondary infected cases. Therefore, the number of prevented secondary infections is R_e (i.e., the best-case scenario point's y-axis value).

Another extreme scenario is the worst-case scenario, also noted by a point in Appendix Figure 2. Under this worst-case scenario, the PCR sample was collected at the moment when the infectious period ends on day 10 (i.e., the worst-case scenario point's x-axis value). Due to such a delayed sampling timing, the number of preventable secondary infections is zero (i.e., the worst-case scenario point's y-axis value) even if the PCR test is available immediately. This is because the confirmed case has already produced secondary infected cases (with the magnitude of R_e) and hence would not produce any more secondary infected cases.

Our decision models assumed more realistic "second-best case scenario" and "second-worst case scenario." This is mainly because we assumed that time lag between screening timing and isolation timing was 0.5 day. Under this more realistic "second-best case scenario," the PCR sample collection timing is the same as the best-case scenario explained above, at the moment when an infectious period starts (i.e., 0 on the x-axis). However, during the time lag before an isolation, the infected case has already produced secondary infection with the magnitude of $R_e \times (0.5 \div 10)$. Still, the PCR test prevented secondary infection with the magnitude of $R_e \times (10 - 0.5) \div 10$, which is the second-best case scenario point's y-axis value. For simplicity, these calculations assumed that the first generation confirmed case discharges a constant number of viruses during the infectious period.

Under the second-worst-case scenario, the number of preventable secondary infections is 0 (i.e., the second-worst-case scenario point's y-axis value), even though the PCR sampling timing is 0.5 day earlier than the worst-case scenario. This is because when the confirmed case is isolated, this first generation confirmed case stops producing secondary infections.

Accounting for all possible scenarios with any prevented secondary infected cases, the sum of the prevented secondary infected cases is equal to the triangular area (with darker shadow in black and white/red-and-blue stripes) defined by the second-best-case scenario point, the second-worst-case scenario point and the origin point in Appendix Figure 2, i.e., $0.5 \times (Re \times [(10 - 0.5) \div 10]) \times 9.5$. Thus, the average number of prevented secondary infected cases per day, during the 10-day infectious period, is estimated as $0.5 \times (Re \times [(10 - 0.5) \div 10]) \times 9.5 \times 1/10$.

As explained above, the average number of prevented secondary infected cases is affected by an infectious period that varies among test positives. The US Centers for Disease Control and Prevention (CDC) guideline recommended different isolation periods depending on the three severity levels among test positives (*24*), which are different from the three severity levels among hospitalized in Japan described earlier. This CDC guideline recommended isolation periods of 5, 10, and 20 days, after symptom onset. Since the infectious period is reported as 2 days before symptom onset (*24*), the infectious periods were assumed to be 7, 12, and 22 days in our decision models.

The weighted average of the infectious periods was estimated by assigning the probability for each of three infectious periods. Regarding the mild cases with a 7-day infectious period, its probability was assumed to be equal to that of isolation among test positives (e.g., 82% under a base-case analysis). For severe cases with a 12-day infectious period, its probability was assumed to be equal to that of hospitalization among test positives, excluding the severe level among the hospitalized (e.g., 18% × 90% under a base-case analysis). Concerning immunocompromised cases with a 22-day infectious period, its probability was assumed to be equal to that of hospitalized with the severe level among test positives (e.g., 18% × 10% under a base-case analysis). Using these assumptions, the weighted average of the infectious periods was estimated to be 8.08 days under the base-case analysis, which was slightly shorter than an estimate of 10 days by Johansson and colleagues (*13*).

Consequently, the average number of prevented secondary infected cases during a certain infectious period (T) is estimated as $0.5 \times (\mathrm{Re} \times [(T - 0.5)/T]) \times (T - 0.5) \times (1/T)$. Under the base case analysis (when R_e is 1.3 and T is 8.08), the estimate of the prevented secondary infection was 0.57. Since we assume that the secondary infected case has the same values of hospitalization and mortality rates as a first generation confirmed case stated earlier, the benefit of preventing secondary infection was estimated with the equation below.

Benefit of preventing secondary infection = 0.57 × 0.54 × (value of hospitalization + value of mortality) × ratio of hospitalization/mortality rates among persons $\geq$80 years of age; thus, 0.57 × 0.54 × ($3,489 + $1,028) × 19 = $26,415 under the base-case analysis.

Finally, the total benefit of finding one confirmed case by a screening was estimated with the equation below.

Total benefit of finding one confirmed infected case by a screening (Bnft_per_case in Decision tree) = [Benefit of reducing hospitalization and mortality rate for a first generation confirmed case]

+ [Benefit of preventing secondary infection] = [$46,343] + [$26,415] = $72,758 under the base-case analysis

Loss of Missing an Infected Case (Test False-Negative Case)

Our study also modeled the loss due to missing a first-generation infected case, i.e., a test false negative case, besides the benefit of finding an infected case explained above. Our model estimated how many second-generation infected cases were produced by a first-generation infected case that was not detected by our screening test for each day from day 1 to day 4. In other words, in our decision model's terminal node, the benefit of finding one infected case was reduced by the loss due to an infected case that already produced a second-generation infected case.

Appendix Figure 3, panel A assumed a 10-day infectious period, following the assumptions in Appendix Figure 2 above. Under Appendix Figure 3, panel B, an infectious period is expressed as "t," which was assigned a triangular distribution in our probabilistic analysis explained earlier.

Appendix Figure 3, panel A indicates that a first-generation infected case produces second-generation infected cases with the magnitude of R_e (i.e., triangular area = $(1/2) \times (R_e/5) \times 10$) during the 10 infectious period. This magnitude is assumed to decline from day 1 to day 10, illustrated by a downslope. Since we do not know when an infected case became infectious, we assumed that the infected case can be from day 1 to day 10, with a 10% probability for each day.

Therefore, on day 1, if a first-generation infected case is missed by the false-negative result of a screening test, on the average, this “missed” first-generation infected case produces second-generation infected cases with the magnitude of [(a1+a2+a3+ ⋯+a10)/10] (Appendix Figure 3, panel A).

Namely, the number of newly produced second-generation infected cases is $(1/10) \times (1/2) \times (R_e/5) \times (10) = (R_e/10)$

This magnitude is equivalent to [(a1+a2+a3+ ⋯+at)/t] in Appendix Figure 3, panel A, in which $(1/t) \times (1/2) \times (R_e/(t/2)) \times (t) = (Re/t)$, expressed as (Inf_2nd_D1) in Appendix Figure 1.

On day 2, all first-generation infected cases were assumed to shift rightward in Appendix Figure 3, since these infected cases aged by 1 day. As a result, in Appendix Figure 3, the triangular area on day 2 became smaller in magnitude than that on day 1. The difference in area between day 1 and day 2 was equivalent to the far left trapezoid area of a1 in Appendix Figure 3.

Thus, on day 2, if a first-generation infected case is missed by the false-negative result of a screening test, on the average, this “missed” first-generation infected case produces second-generation infected cases with the magnitude of [(a2+a3+a4+⋯+a10)/9] in Appendix Figure 3, panel A.

Namely, the number of newly produced second-generation infected cases = $(1/9) \times (1/2) \times [(R_e/5) \times (9/10)] \times 9 = (R_e/10) \times (9/10)$. This magnitude is equivalent to [(a2+a3+ ⋯+at)/(t – 1)] in Appendix Figure 3, panel B, in which $1/(t-1) \times (1/2) \times [(R_e/(t/2)) \times (t-1) \times (1/t)] \times (t-1) = (R_e/t) \times (t-1) \times (1/t)$, expressed as (Inf_2nd_D2) in Appendix Figure 1.

Likewise, on day 3, if a first-generation infected case is missed by the false-negative result of a screening test, on the average, this “missed” first-generation infected case produces second-generation infected cases with the magnitude of $[(a3+a4+\cdots+a10)/8]$ in Appendix Figure 3, panel A.

Namely, the number of newly produced second-generation infected cases is $(1/8) \times (1/2) \times [(R_e/5) \times (8/10)] \times 8 = (R_e/10) \times (8/10)$. This magnitude is equivalent to $[((a3+a4+ \cdots+at)/(t-2)]$ in Appendix Figure 3, panel B, in which $1/(t-2) \times (1/2) \times [(R_e/(t/2)) \times (t-2) \times (1/t)] \times (t-2) = (R_e/t) \times (t-2) \times (1/t)$, expressed as (Inf_2nd_D3) in Appendix Figure 1.

Similarly, on day 4, if a first-generation infected case is missed by the false-negative result of a screening test, on the average, this "missed" first-generation infected case produces second-generation infected cases with the magnitude of $[(a4+a5+\cdots+a10)/7]$ in Appendix Figure 3, panel A. Namely, the number of newly produced second-generation infected cases is $(1/7) \times (1/2) \times [(R_e/5) \times (7/10)] \times 7 = (R_e/10) \times (7/10)$.

This magnitude is equivalent to $[((a4+a5+ \cdots+at)/(t-3))$ in Appendix Figure 3, panel B, in which $(1/(t-3)) \times (1/2) \times [(R_e/(t-3)) \times (t-3) \times (1/t)] \times (t-3) = (R_e/t) \times (t-3) \times (1/t)$, expressed as (Inf_2nd_D4) in Appendix Figure 1.

Additionally, our study assumed that the value of missing one infected case (Loss_per_case) is equal to that of finding one infected case (Bnft_per_case) under each screening option, under the base case analysis. Our one-way sensitivity analysis assumed the ratio of Loss/Benefit to range from 0 to 2. The results of this one-way sensitivity analysis was robust (Appendix Table 28).

"Total benefit of finding one confirmed case by a screening (Bnft_per_case in Decision tree)]" was defined earlier. In our modeling, on day 2, even when one infected case was detected by a screening test, the benefit was discounted by allowing this case to produce secondary infected cases on day 1, expressed as below, when the infectious period is t:

$$\text{Bnft\_per\_case} \times (1 - (R_e/t))$$

Under the base case analysis, this equation is expressed as below:

$$\text{Bnft\_per\_case} - \text{Loss\_per\_case} \times \text{Inf\_2nd\_D1}$$

where the term of (R_e/t) is explained with Appendix Figure 3, panel B, and defined as Inf_2nd_D1 earlier.

Likewise, on day 3, even when one infected case was detected by a screening test, the benefit was discounted by allowing this case to produce secondary infected cases on day 1 and day 2, expressed as below, when the infectious period is t:

$$\text{Bnft\_per\_case} \times (1 - (R_e/t) - (R_e/t) \times (t - 1) \times (1/t))$$

Under the base case analysis, this equation is expressed as below:

$$\text{Bnft\_per\_case} - \text{Loss\_per\_case} \times (\text{Inf\_2nd\_D1} + \text{Inf\_2nd\_D2})$$

where the term of $(R_e/t) \times (t - 1) \times (1/t)$ is explained with Appendix Figure 3, panel B, and defined as Inf_2nd_D2 earlier.

Similarly, on day 4, even when one infected case was detected by a screening test, the benefit was discounted by allowing this case to produce secondary infected cases on day 1, day 2, and day 3, expressed as below, when the infectious period is t:

$$\text{Bnft\_per\_case} \times (1 - (R_e/t) - (R_e/t) \times (t - 1) \times (1/t) - (R_e/t) \times (t - 2) \times (1/t))$$

Under the base case analysis, this equation is expressed as below:

$$\text{Bnft\_per\_case} - \text{Loss\_per\_case} \times (\text{Inf\_2nd\_D1} + \text{Inf\_2nd\_D2} + \text{Inf\_2nd\_D3})$$

where the term of $(R_e/t) \times (t - 2) \times (1/t)$ is explained with Appendix Figure 3, panel B, and defined as Inf_2nd_D3 earlier.

On day 4, when one infected case was still not detected by a screening test, the loss of missing this infected case is expressed as below, when the infectious period is t:

$$-\text{Bnft\_per\_case} \times ((R_e/t) + (R_e/t) \times (t - 1) \times (1/t) + (R_e/t) \times (t - 2) \times (1/t) + (R_e/t) \times (t - 3) \times (1/t))$$

Under the base case analysis, this equation is expressed as below:

$$- \text{Loss\_per\_case} \times (\text{Inf\_2nd\_D1} + \text{Inf\_2nd\_D2} + \text{Inf\_2nd\_D3} + \text{Inf\_2nd\_D4})$$

where the term of $(R_e/t) \times (t - 3) \times (1/t)$ is explained with Appendix Figure 3, panel B, and defined as Inf_2nd_D4 earlier.

Relationship between Prevalence and Incidence

Our decision model assumed the prevalence as a function of the incidence. To define a relatively simplified relationship between the COVID-19 disease prevalence and incidence, we assumed the hypothetical scenario among N residents in the area around the facility illustrated in Appendix Figure 4. In this figure, the top line shows a date from the first case being infected. This infected case was assumed to be infectious from day 3 to day 13, i.e., for a 10-day period (*13*). Only during this 10-day infectious period, could an infected case be detected by antigen tests and PCR tests, i.e., counted as a part of incidence (presented as the bottom line in this figure) and prevalence (2nd line from the bottom in this figure). Therefore, on day 3, both the prevalence and the incidence were one [per N residents].

The first infected case was also called the 1st generation in this figure. During the 10-day infectious period, the first infected case transmits viruses to produce 2nd generation infected cases at the magnitude of R, which is a reproduction number. For simplicity, the 2nd generation infected cases were produced at the midpoint of the 10-day infection period, i.e., day 8. Thus, on day 8 the incidence was R [per N residents] and the prevalence was “R (2nd generation) plus one (1st generation is still infectious).”

Similarly, the 3rd generation infected cases were produced at the midpoint of the 10-day infection period, i.e., day 13. Since each of R infected cases among the 2nd generation produces newly infected cases by R, the 3rd generation infected cases were “R-squared (R^2)” in number. Hence, on day 13, the incidence was “R^2” [per N residents] and the prevalence was “R^2 (3rd generation) plus R (2nd generation) plus one (the final infectious day of 1st generation).”

Likewise, on day 18, the incidence was “R^3” [per N residents] and the prevalence was “R^3 (4th generation) plus R^2 (3rd generation) plus R (2nd generation).” On day 23, the incidence was “R^4” [per N residents] and the prevalence was “R^4 plus R^3 plus R^2.”

After day 13, a proxy for the relationship between prevalence and incidence is mathematically expressed as below:

A proxy of “Prevalence/Incidence” = $(1 + R + R^2)/ (R^2)$

This proxy ratio was 2.36 in our base case analysis, where the reproduction number (R in this figure) is at the point estimate of 1.3. When the reproduction number ranged from 0.9 to 2, this ratio declined from 3.35 to 1.75. This point estimate and this range of the reproduction number followed Neilan et al (*25*).

In the decision tree, the disease prevalence (pvl_fx_Re) was defined as a multiplication of the disease incidence and a proxy of “Prevalence/Incidence” expressed above.

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Appendix Table 1. Percentage of three severity levels among COVID-19 hospitalized cases in Japan*

Severity level	Mode (point estimate) of severe cases	Minimum severe cases	Maximum severe cases
Light	58%	61%	52%
Moderate	32%	34%	29%

*The mode (point estimate) of severe cases was 10%; minimum was 5% and maximum was 19%.

Appendix Table 2. Total payment rates per hospitalized case based on COVID-19 severity, Japan*

Severity level	Average length of stay, d†	FFS based payment rate per day per case†	Supplemental payment rate per day per case‡	Total hospitalization cost per case
Light	10.9	$409	$538	$10,322
Moderate	15.5	$606	$538	$17,731
Severe	22	$1,076	$2,435	$77,229

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). FFS, fee for service.

†Average length of stay and FFS from Global Health Consulting (*16*).

‡Supplemental payment rate from Ministry of Health, Labour and Welfare (*17*).

Appendix Table 3. Age and sex distribution among deaths due to COVID-19, Japan*

	Cumulative deaths up to 2021 Dec 27			Cumulative deaths up to 2022 Aug 1		
Age	M	F	Not disclosed	M	F	Not disclosed
<10	0	0	0	4	4	0
10–19	2	1	0	6	2	1
20–29	15	5	2	26	8	2
30–39	54	19	2	74	30	5
40–49	188	53	7	254	73	9
50–59	569	129	15	725	182	30
60–69	988	292	34	1,369	406	55
70–79	2,333	1,056	74	3,596	1,535	134
80–89	3,134	2,519	252	5,177	3,836	209
≥90	1,096	1,814	33	2,129	3,459	164

*Data collected from National Institute of Population and Social Security Research (*19*).

Appendix Table 4. Life expectancies by sex at specific ages in Japan in 2020*

	Life expectancy, y	
Current age, y	M	F
5	76.83	82.93
15	66.89	72.98
25	57.12	63.12
35	47.40	53.28
45	37.80	43.56
55	28.58	34.09
65	20.05	24.91
75	12.63	16.25
85	6.67	8.76
90	4.59	5.92

*Data collected from Ministry of Health, Labour and Welfare (*20*).

Appendix Table 5. Mortality rates among persons testing SARS-CoV-2 positive during different waves, Japan (*23*)

	Up to the 6th wave†		Up to the 5th wave‡		During the 6th wave§	
Time lag*	Date range	Mortality rate, %	Date range	Mortality rate, %	Date range	Mortality rate, %
Persons >80 y						
0	2020 Sep 8–2022 May 31	0.35	2020 Sep 8–2022 Jan 4	1.03	4 Jan–31 May 2022	0.18
1 week	2020 Sep 8–2022 Jun 7	0.35	2020 Sep 8–2022 Jan 11	1.03	4 Jan–7 Jun 2022	0.18
2 weeks	2020 Sep 8–2022 Jun 14	0.35	2020 Sep 8–2022 Jan 18	1.03	4 Jan–14 Jun 2022	0.18
3 weeks	2020 Sep 8–2022 Jun 21	0.35	2020 Sep 8–2022 Jan 25	1.04	4 Jan–21 Jun 2022	0.19
4 weeks	2020 Sep 8–2022 Jun 28	0.35	2020 Sep 8–2022 Feb 1	1.05	4 Jan–28 Jun 2022	0.19
Persons ≥80 y						
0	2020 Sep 8–2022 May 31	6.70	2020 Sep 8–2022 Jan 4	15.34	4 Jan–31 May 2022	4.01
1 week	2020 Sep 8–2022 Jun 7	6.74	2020 Sep 8–2022 Jan 11	15.34	4 Jan–7 Jun 2022	4.06
2 weeks	2020 Sep 8–2022 Jun 14	6.77	2020 Sep 8–2022 Jan 18	15.36	4 Jan–14 Jun 2022	4.10
3 weeks	2020 Sep 8–2022 Jun 21	6.81	2020 Sep 8–2022 Jan 25	15.45	4 Jan–21 Jun 2022	4.16
4 weeks	2020 Sep 8–2022 Jun 28	6.84	2020 Sep 8–2022 Feb 1	15.71	4 Jan–28 Jun 2022	4.19

*Time lag is the period between positive tests (denominator) and death (numerator); date range indicates range during which deaths were included.

†September 8, 2020–May 31, 2022.

‡September 8, 2020–January 4, 2022.

§January 4–May 31, 2022.

Appendix Table 6. One-way sensitivity analysis for sensitivity of wastewater surveillance used in an economic evaluation of wastewater surveillance combined with clinical COVID-19 screening tests, Japan*

	Option 1†			Option 2†			Relative value of option 2		
Sensitivity	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
0.46	$67.05	$14.09	0.21	$53.61	$6.69	0.12	–$13.44	–$7.40	2
0.47	$67.05	$14.09	0.21	$53.61	$7.05	0.13	–$13.44	–$7.04	2
0.48	$67.05	$14.09	0.21	$53.61	$7.40	0.14	–$13.44	–$6.69	2
0.49	$67.05	$14.09	0.21	$53.61	$7.74	0.14	–$13.44	–$6.35	2
0.5	$67.05	$14.09	0.21	$53.61	$8.07	0.15	–$13.44	–$6.02	2
0.51	$67.05	$14.09	0.21	$53.61	$8.39	0.16	–$13.43	–$5.70	2
0.52	$67.05	$14.09	0.21	$53.61	$8.70	0.16	–$13.43	–$5.39	2
0.53	$67.05	$14.09	0.21	$53.61	$8.99	0.17	–$13.43	–$5.10	3
0.54	$67.05	$14.09	0.21	$53.61	$9.28	0.17	–$13.43	–$4.81	3
0.55	$67.05	$14.09	0.21	$53.61	$9.55	0.18	–$13.43	–$4.54	3
0.56	$67.05	$14.09	0.21	$53.61	$9.81	0.18	–$13.43	–$4.28	3
0.57	$67.05	$14.09	0.21	$53.61	$10.07	0.19	–$13.43	–$4.02	3
0.58	$67.05	$14.09	0.21	$53.61	$10.31	0.19	–$13.43	–$3.78	4
0.59	$67.05	$14.09	0.21	$53.61	$10.55	0.20	–$13.43	–$3.54	4
0.6	$67.05	$14.09	0.21	$53.61	$10.77	0.20	–$13.43	–$3.32	4
0.61	$67.05	$14.09	0.21	$53.61	$10.99	0.20	–$13.43	–$3.10	4
0.62	$67.05	$14.09	0.21	$53.61	$11.20	0.21	–$13.43	–$2.89	5
0.63	$67.05	$14.09	0.21	$53.61	$11.39	0.21	–$13.43	–$2.70	5
0.64	$67.05	$14.09	0.21	$53.61	$11.58	0.22	–$13.43	–$2.51	5
0.65	$67.05	$14.09	0.21	$53.61	$11.77	0.22	–$13.43	–$2.32	6
0.66	$67.05	$14.09	0.21	$53.61	$11.94	0.22	–$13.43	–$2.15	6
0.67	$67.05	$14.09	0.21	$53.61	$12.11	0.23	–$13.43	–$1.98	7
0.68	$67.05	$14.09	0.21	$53.61	$12.26	0.23	–$13.43	–$1.83	7
0.69	$67.05	$14.09	0.21	$53.61	$12.41	0.23	–$13.43	–$1.68	8
0.7	$67.05	$14.09	0.21	$53.61	$12.56	0.23	–$13.43	–$1.53	9
0.71	$67.05	$14.09	0.21	$53.61	$12.69	0.24	–$13.43	–$1.40	10
0.72	$67.05	$14.09	0.21	$53.61	$12.82	0.24	–$13.43	–$1.27	11
0.73	$67.05	$14.09	0.21	$53.61	$12.95	0.24	–$13.43	–$1.14	12
0.74	$67.05	$14.09	0.21	$53.61	$13.06	0.24	–$13.43	–$1.03	13
0.75	$67.05	$14.09	0.21	$53.61	$13.17	0.25	–$13.43	–$0.92	15
0.76	$67.05	$14.09	0.21	$53.61	$13.28	0.25	–$13.43	–$0.81	17

	Option 1†			Option 2†			Relative value of option 2		
Sensitivity	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
0.77	$67.05	$14.09	0.21	$53.61	$13.38	0.25	–$13.43	–$0.71	19
0.78	$67.05	$14.09	0.21	$53.61	$13.47	0.25	–$13.43	–$0.62	22
0.79	$67.05	$14.09	0.21	$53.61	$13.56	0.25	–$13.43	–$0.53	25
0.8	$67.05	$14.09	0.21	$53.61	$13.64	0.25	–$13.43	–$0.45	30
0.81	$67.05	$14.09	0.21	$53.61	$13.72	0.26	–$13.43	–$0.37	36
0.82	$67.05	$14.09	0.21	$53.61	$13.79	0.26	–$13.43	–$0.30	45
0.83	$67.05	$14.09	0.21	$53.61	$13.86	0.26	–$13.43	–$0.23	58
0.84	$67.05	$14.09	0.21	$53.61	$13.92	0.26	–$13.43	–$0.17	80

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for sensitivity of wastewater surveillance was sns_WW. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 7. One-way sensitivity analysis for sensitivity of clinical PCR testing used in an economic evaluation of wastewater surveillance combined with clinical COVID-19 screening tests, Japan*

	Option 1†			Option 2†			Relative value of option 2		
Sensitivity	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
0.64	$67.05	$12.36	0.18	$53.61	$11.94	0.22	–$13.43	–$0.42	32
0.65	$67.05	$12.56	0.19	$53.61	$11.94	0.22	–$13.43	–$0.62	22
0.66	$67.05	$12.76	0.19	$53.61	$11.94	0.22	–$13.43	–$0.82	16
0.67	$67.05	$12.95	0.19	$53.61	$11.94	0.22	–$13.43	–$1.01	13
0.68	$67.05	$13.13	0.20	$53.61	$11.94	0.22	–$13.43	–$1.19	11
0.69	$67.05	$13.30	0.20	$53.61	$11.94	0.22	–$13.43	–$1.36	10
0.7	$67.05	$13.47	0.20	$53.61	$11.94	0.22	–$13.43	–$1.53	9
0.71	$67.05	$13.64	0.20	$53.61	$11.94	0.22	–$13.43	–$1.70	8
0.72	$67.05	$13.79	0.21	$53.61	$11.94	0.22	–$13.43	–$1.85	7
0.73	$67.05	$13.94	0.21	$53.61	$11.94	0.22	–$13.43	–$2.00	7
0.74	$67.05	$14.09	0.21	$53.61	$11.94	0.22	–$13.43	–$2.15	6
0.75	$67.05	$14.23	0.21	$53.61	$11.94	0.22	–$13.43	–$2.29	6
0.76	$67.05	$14.37	0.21	$53.61	$11.94	0.22	–$13.43	–$2.43	6
0.77	$67.05	$14.49	0.22	$53.61	$11.94	0.22	–$13.43	–$2.56	5
0.78	$67.05	$14.62	0.22	$53.61	$11.94	0.22	–$13.43	–$2.68	5
0.79	$67.05	$14.74	0.22	$53.61	$11.94	0.22	–$13.43	–$2.80	5
0.8	$67.05	$14.85	0.22	$53.61	$11.94	0.22	–$13.43	–$2.91	5
0.81	$67.05	$14.97	0.22	$53.61	$11.94	0.22	–$13.43	–$3.03	4
0.82	$67.05	$15.07	0.22	$53.61	$11.94	0.22	–$13.43	–$3.13	4
0.83	$67.05	$15.17	0.23	$53.61	$11.94	0.22	–$13.43	–$3.23	4

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for sensitivity of PCR testing was sns_PCR. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 8. One-way sensitivity analysis for the ratio of sensitivity of antigen test compared with PCR test in an economic evaluation of wastewater surveillance combined with clinical COVID-19 screening tests, Japan*

	Option 1†			Option 2†			Relative value of option 2		
Sensitivity	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
0.54	$67.05	$9.47	0.14	$53.61	$11.94	0.22	–$13.43	$2.47	−5.43
0.55	$67.05	$9.76	0.15	$53.61	$11.94	0.22	–$13.43	$2.18	−6.16
0.56	$67.05	$10.04	0.15	$53.61	$11.94	0.22	–$13.43	$1.90	−7.07
0.57	$67.05	$10.31	0.15	$53.61	$11.94	0.22	–$13.43	$1.63	−8.26
0.58	$67.05	$10.58	0.16	$53.61	$11.94	0.22	–$13.43	$1.36	−9.87
0.59	$67.05	$10.84	0.16	$53.61	$11.94	0.22	–$13.43	$1.10	−12.16
0.6	$67.05	$11.08	0.17	$53.61	$11.94	0.22	–$13.43	$0.86	−15.69
0.61	$67.05	$11.32	0.17	$53.61	$11.94	0.22	–$13.43	$0.62	−21.82
0.62	$67.05	$11.56	0.17	$53.61	$11.94	0.22	–$13.43	$0.38	−35.05
0.63	$67.05	$11.78	0.18	$53.61	$11.94	0.22	–$13.43	$0.16	−84.77
0.64	$67.05	$12.00	0.18	$53.61	$11.94	0.22	–$13.43	–$0.06	228
0.65	$67.05	$12.21	0.18	$53.61	$11.94	0.22	–$13.43	–$0.27	50
0.66	$67.05	$12.41	0.19	$53.61	$11.94	0.22	–$13.43	–$0.47	28
0.67	$67.05	$12.61	0.19	$53.61	$11.94	0.22	–$13.43	–$0.67	20
0.68	$67.05	$12.80	0.19	$53.61	$11.94	0.22	–$13.43	–$0.86	16
0.69	$67.05	$12.98	0.19	$53.61	$11.94	0.22	–$13.43	–$1.04	13
0.7	$67.05	$13.16	0.20	$53.61	$11.94	0.22	–$13.43	–$1.22	11
0.71	$67.05	$13.33	0.20	$53.61	$11.94	0.22	–$13.43	–$1.39	10
0.72	$67.05	$13.49	0.20	$53.61	$11.94	0.22	–$13.43	–$1.55	9
0.73	$67.05	$13.65	0.20	$53.61	$11.94	0.22	–$13.43	–$1.71	8
0.74	$67.05	$13.80	0.21	$53.61	$11.94	0.22	–$13.43	–$1.86	7
0.75	$67.05	$13.95	0.21	$53.61	$11.94	0.22	–$13.43	–$2.01	7
0.76	$67.05	$14.09	0.21	$53.61	$11.94	0.22	–$13.43	–$2.15	6
0.77	$67.05	$14.23	0.21	$53.61	$11.94	0.22	–$13.43	–$2.29	6
0.78	$67.05	$14.36	0.21	$53.61	$11.94	0.22	–$13.43	–$2.42	6
0.79	$67.05	$14.48	0.22	$53.61	$11.94	0.22	–$13.43	–$2.55	5
0.8	$67.05	$14.61	0.22	$53.61	$11.94	0.22	–$13.43	–$2.67	5
0.81	$67.05	$14.72	0.22	$53.61	$11.94	0.22	–$13.43	–$2.78	5
0.82	$67.05	$14.84	0.22	$53.61	$11.94	0.22	–$13.43	–$2.90	5
0.83	$67.05	$14.95	0.22	$53.61	$11.94	0.22	–$13.43	–$3.01	4
0.84	$67.05	$15.05	0.22	$53.61	$11.94	0.22	–$13.43	–$3.11	4
0.85	$67.05	$15.15	0.23	$53.61	$11.94	0.22	–$13.43	–$3.21	4

	Option 1†			Option 2†			Relative value of option 2		
Sensitivity	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
0.86	$67.05	$15.25	0.23	$53.61	$11.94	0.22	–$13.43	–$3.31	4
0.87	$67.05	$15.34	0.23	$53.61	$11.94	0.22	–$13.43	–$3.40	4
0.88	$67.05	$15.43	0.23	$53.61	$11.94	0.22	–$13.43	–$3.49	4
0.89	$67.05	$15.51	0.23	$53.61	$11.94	0.22	–$13.43	–$3.57	4
0.9	$67.05	$15.60	0.23	$53.61	$11.94	0.22	–$13.43	–$3.66	4
0.91	$67.05	$15.68	0.23	$53.61	$11.94	0.22	–$13.43	–$3.74	4
0.92	$67.05	$15.75	0.23	$53.61	$11.94	0.22	–$13.43	–$3.81	4
0.93	$67.05	$15.82	0.24	$53.61	$11.94	0.22	–$13.43	–$3.88	3
0.94	$67.05	$15.89	0.24	$53.61	$11.94	0.22	–$13.43	–$3.95	3
0.95	$67.05	$15.96	0.24	$53.61	$11.94	0.22	–$13.43	–$4.02	3
0.96	$67.05	$16.03	0.24	$53.61	$11.94	0.22	–$13.43	–$4.09	3
0.97	$67.05	$16.09	0.24	$53.61	$11.94	0.22	–$13.43	–$4.15	3

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for the ratio of sensitivity of antigen test against PCR test was sns_Ag_ratio_PCR. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 9. One-way sensitivity analysis for sensitivity of clinical PCR test subsequent to a positive antigen test in an economic evaluation of wastewater surveillance combined with clinical COVID-19 screening tests, Japan*

	Option 1†			Option 2†			Relative value of option 2		
Sensitivity	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
0.64	$67.06	$7.91	0.12	$53.62	$5.39	0.10	–$13.44	–$2.52	5
0.7	$67.05	$9.39	0.14	$53.62	$6.93	0.13	–$13.44	–$2.46	5
0.8	$67.05	$11.42	0.17	$53.62	$9.09	0.17	–$13.43	–$2.33	6
0.9	$67.05	$13.00	0.19	$53.62	$10.77	0.20	–$13.43	–$2.22	6
0.99	$67.05	$14.09	0.21	$53.61	$11.94	0.22	–$13.43	–$2.15	6
0.999	$67.05	$14.19	0.21	$53.61	$12.04	0.22	–$13.43	–$2.14	6

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for sensitivity of PCR test subsequent to a positive antigen test was sns_PCR_2nd. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 10. One-way sensitivity analysis for specificity of clinical PCR test used in an economic evaluation of wastewater surveillance combined with clinical COVID-19 screening tests, Japan*

	Option 1†			Option 2†			Relative value of option 2		
Specificity	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
0.960	$67.05	$14.06	0.21	$56.77	$11.80	0.21	–$10.27	–$2.26	5
0.961	$67.05	$14.06	0.21	$56.55	$11.82	0.21	–$10.50	–$2.25	5
0.962	$67.05	$14.06	0.21	$56.32	$11.83	0.21	–$10.73	–$2.24	5
0.963	$67.05	$14.07	0.21	$56.10	$11.84	0.21	–$10.95	–$2.23	5
0.964	$67.05	$14.07	0.21	$55.87	$11.85	0.21	–$11.18	–$2.22	5
0.965	$67.05	$14.07	0.21	$55.64	$11.86	0.21	–$11.40	–$2.21	5
0.966	$67.05	$14.07	0.21	$55.42	$11.87	0.21	–$11.63	–$2.20	5
0.967	$67.05	$14.08	0.21	$55.19	$11.88	0.22	–$11.85	–$2.19	5
0.968	$67.05	$14.08	0.21	$54.97	$11.89	0.22	–$12.08	–$2.19	6
0.969	$67.05	$14.08	0.21	$54.74	$11.90	0.22	–$12.31	–$2.18	6
0.97	$67.05	$14.08	0.21	$54.52	$11.91	0.22	–$12.53	–$2.17	6
0.971	$67.05	$14.08	0.21	$54.29	$11.92	0.22	–$12.76	–$2.17	6
0.972	$67.05	$14.09	0.21	$54.07	$11.93	0.22	–$12.98	–$2.16	6
0.973	$67.05	$14.09	0.21	$53.84	$11.93	0.22	–$13.21	–$2.16	6
0.974	$67.05	$14.09	0.21	$53.61	$11.94	0.22	–$13.43	–$2.15	6
0.975	$67.05	$14.09	0.21	$53.39	$11.95	0.22	–$13.66	–$2.15	6
0.976	$67.05	$14.09	0.21	$53.16	$11.95	0.22	–$13.88	–$2.14	6
0.977	$67.05	$14.10	0.21	$52.94	$11.96	0.23	–$14.11	–$2.14	7
0.978	$67.05	$14.10	0.21	$52.71	$11.96	0.23	–$14.34	–$2.13	7
0.979	$67.05	$14.10	0.21	$52.49	$11.97	0.23	–$14.56	–$2.13	7
0.98	$67.05	$14.10	0.21	$52.26	$11.97	0.23	–$14.79	–$2.13	7
0.981	$67.05	$14.10	0.21	$52.03	$11.97	0.23	–$15.01	–$2.13	7
0.982	$67.05	$14.10	0.21	$51.81	$11.98	0.23	–$15.24	–$2.12	7
0.983	$67.05	$14.10	0.21	$51.58	$11.98	0.23	–$15.46	–$2.12	7
0.984	$67.05	$14.10	0.21	$51.36	$11.98	0.23	–$15.69	–$2.12	7
0.985	$67.05	$14.11	0.21	$51.13	$11.99	0.23	–$15.92	–$2.12	8
0.986	$67.05	$14.11	0.21	$50.91	$11.99	0.24	–$16.14	–$2.12	8
0.987	$67.05	$14.11	0.21	$50.68	$11.99	0.24	–$16.37	–$2.12	8
0.988	$67.05	$14.11	0.21	$50.45	$11.99	0.24	–$16.59	–$2.12	8
0.989	$67.05	$14.11	0.21	$50.23	$11.99	0.24	–$16.82	–$2.11	8
0.99	$67.05	$14.11	0.21	$50.00	$12.00	0.24	–$17.04	–$2.11	8
0.991	$67.05	$14.11	0.21	$49.78	$12.00	0.24	–$17.27	–$2.11	8

	Option 1†			Option 2†			Relative value of option 2		
Specificity	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
0.992	$67.05	$14.11	0.21	$49.55	$12.00	0.24	–$17.50	–$2.11	8
0.993	$67.05	$14.11	0.21	$49.33	$12.00	0.24	–$17.72	–$2.11	8
0.994	$67.05	$14.11	0.21	$49.10	$12.00	0.24	–$17.95	–$2.11	8
0.995	$67.05	$14.11	0.21	$48.88	$12.00	0.25	–$18.17	–$2.11	9

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for specificity of clinical PCR test was spc_PCR. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 11. One-way sensitivity analysis for specificity of antigen test used in an economic evaluation of wastewater surveillance combined with clinical COVID-19 screening tests, Japan*

	Option 1†			Option 2†			Relative value of option 2		
Specificity	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
0.97	$73.12	$14.05	0.19	$53.61	$11.94	0.22	–$19.51	–$2.11	9
0.971	$72.82	$14.05	0.19	$53.61	$11.94	0.22	–$19.21	–$2.11	9
0.972	$72.52	$14.05	0.19	$53.61	$11.94	0.22	–$18.90	–$2.11	9
0.973	$72.21	$14.05	0.19	$53.61	$11.94	0.22	–$18.60	–$2.11	9
0.974	$71.91	$14.05	0.20	$53.61	$11.94	0.22	–$18.30	–$2.11	9
0.975	$71.61	$14.06	0.20	$53.61	$11.94	0.22	–$17.99	–$2.12	9
0.976	$71.30	$14.06	0.20	$53.61	$11.94	0.22	–$17.69	–$2.12	8
0.977	$71.00	$14.06	0.20	$53.61	$11.94	0.22	–$17.38	–$2.12	8
0.978	$70.69	$14.06	0.20	$53.61	$11.94	0.22	–$17.08	–$2.12	8
0.979	$70.39	$14.07	0.20	$53.61	$11.94	0.22	–$16.78	–$2.13	8
0.98	$70.09	$14.07	0.20	$53.61	$11.94	0.22	–$16.47	–$2.13	8
0.981	$69.78	$14.07	0.20	$53.61	$11.94	0.22	–$16.17	–$2.13	8
0.982	$69.48	$14.07	0.20	$53.61	$11.94	0.22	–$15.86	–$2.13	7

	Option 1†			Option 2†			Relative value of option 2		
Specificity	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
0.983	$69.17	$14.07	0.20	$53.61	$11.94	0.22	–$15.56	–$2.13	7
0.984	$68.87	$14.08	0.20	$53.61	$11.94	0.22	–$15.26	–$2.14	7
0.985	$68.57	$14.08	0.21	$53.61	$11.94	0.22	–$14.95	–$2.14	7
0.986	$68.26	$14.08	0.21	$53.61	$11.94	0.22	–$14.65	–$2.14	7
0.987	$67.96	$14.08	0.21	$53.61	$11.94	0.22	–$14.35	–$2.14	7
0.988	$67.66	$14.09	0.21	$53.61	$11.94	0.22	–$14.04	–$2.15	7
0.989	$67.35	$14.09	0.21	$53.61	$11.94	0.22	–$13.74	–$2.15	6
0.99	$67.05	$14.09	0.21	$53.61	$11.94	0.22	–$13.43	–$2.15	6
0.991	$66.74	$14.09	0.21	$53.61	$11.94	0.22	–$13.13	–$2.15	6
0.992	$66.44	$14.09	0.21	$53.61	$11.94	0.22	–$12.83	–$2.15	6
0.993	$66.14	$14.10	0.21	$53.61	$11.94	0.22	–$12.52	–$2.16	6
0.994	$65.83	$14.10	0.21	$53.61	$11.94	0.22	–$12.22	–$2.16	6
0.995	$65.53	$14.10	0.22	$53.61	$11.94	0.22	–$11.91	–$2.16	6

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for specificity of antigen tests was spc_Ag. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 12. One-way sensitivity analysis of laboratory cost of wastewater surveillance per day per facility in an economic evaluation of wastewater surveillance combined with clinical COVID-19 screening tests, Japan*

	Option 1†			Option 2†			Relative value of option 2		
Laboratory cost	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
$189	$67.05	$14.09	0.21	$47.91	$11.94	0.25	–$19.13	–$2.15	9
$246	$67.05	$14.09	0.21	$49.62	$11.94	0.24	–$17.43	–$2.15	8
$303	$67.05	$14.09	0.21	$51.33	$11.94	0.23	–$15.72	–$2.15	7
$360	$67.05	$14.09	0.21	$53.03	$11.94	0.23	–$14.01	–$2.15	7
$417	$67.05	$14.09	0.21	$54.74	$11.94	0.22	–$12.31	–$2.15	6
$474	$67.05	$14.09	0.21	$56.45	$11.94	0.21	–$10.60	–$2.15	5
$530	$67.05	$14.09	0.21	$58.16	$11.94	0.21	–$8.89	–$2.15	4
$587	$67.05	$14.09	0.21	$59.86	$11.94	0.20	–$7.18	–$2.15	3
$644	$67.05	$14.09	0.21	$61.57	$11.94	0.19	–$5.48	–$2.15	3
$701	$67.05	$14.09	0.21	$63.28	$11.94	0.19	–$3.77	–$2.15	2
$750	$67.05	$14.09	0.21	$64.74	$11.94	0.18	–$2.30	–$2.15	1.07
$755	$67.05	$14.09	0.21	$64.89	$11.94	0.18	–$2.15	–$2.15	1.00
$756	$67.05	$14.09	0.21	$64.92	$11.94	0.18	–$2.12	–$2.15	0.99
$758	$67.05	$14.09	0.21	$64.98	$11.94	0.18	–$2.06	–$2.15	0.96

*Cost per facility per day reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for laboratory cost of wastewater surveillance was C_ww_unit_per_test. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option’s ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2’s relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2’s relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 13. One-way sensitivity analysis of labor cost to sample wastewater per day per facility in an economic evaluation of wastewater surveillance combined with clinical COVID-19 screening tests, Japan*

	Option 1†			Option 2†			Relative value of option 2		
Labor cost	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
$152	$67.05	$14.09	0.21	$24.09	$11.94	0.50	–$42.95	–$2.15	20

	Option 1†			Option 2†			Relative value of option 2		
Labor cost	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
$341	$67.05	$14.09	0.21	$29.77	$11.94	0.40	–$37.27	–$2.15	17
$531	$67.05	$14.09	0.21	$35.45	$11.94	0.34	–$31.60	–$2.15	15
$720	$67.05	$14.09	0.21	$41.13	$11.94	0.29	–$25.92	–$2.15	12
$909	$67.05	$14.09	0.21	$46.81	$11.94	0.26	–$20.24	–$2.15	9
$1,099	$67.05	$14.09	0.21	$52.49	$11.94	0.23	–$14.56	–$2.15	7
$1,288	$67.05	$14.09	0.21	$58.17	$11.94	0.21	–$8.88	–$2.15	4
$1,477	$67.05	$14.09	0.21	$63.85	$11.94	0.19	–$3.20	–$2.15	1.49
$1,510	$67.05	$14.09	0.21	$64.83	$11.94	0.18	–$2.21	–$2.15	1.03
$1,515	$67.05	$14.09	0.21	$64.98	$11.94	0.18	–$2.06	–$2.15	0.96
$1,580	$67.05	$14.09	0.21	$66.93	$11.94	0.18	–$0.11	–$2.15	0.05
$1,585	$67.05	$14.09	0.21	$67.08	$11.94	0.18	$0.04	–$2.15	−0.02
$1,666	$67.05	$14.09	0.21	$69.53	$11.94	0.17	$2.48	–$2.15	−1.15
$1,856	$67.05	$14.09	0.21	$75.20	$11.94	0.16	$8.16	–$2.15	−3.79
$2,045	$67.05	$14.09	0.21	$80.88	$11.94	0.15	$13.84	–$2.15	−6.43

*Cost per facility per day reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for labor cost of wastewater surveillance was C_ww_f_lbr. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 14. One-way sensitivity analysis of cost for antigen test in an economic evaluation of wastewater surveillance combined with clinical COVID-19 screening tests, Japan*

Antigen test	Option 1†			Option 2†			Relative value of option 2		
cost	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
$10	$43.05	$14.09	0.33	$53.61	$11.94	0.22	$10.56	–$2.15	−4.91
$11	$47.05	$14.09	0.30	$53.61	$11.94	0.22	$6.56	–$2.15	−3.05
$12	$51.05	$14.09	0.28	$53.61	$11.94	0.22	$2.56	–$2.15	−1.19

Antigen test	Option 1†			Option 2†			Relative value of option 2		
cost	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
$13	$55.05	$14.09	0.26	$53.61	$11.94	0.22	–$1.44	–$2.15	0.67
$13.18	$55.77	$14.09	0.25	$53.61	$11.94	0.22	–$2.16	–$2.15	1.00
$14	$59.05	$14.09	0.24	$53.61	$11.94	0.22	–$5.43	–$2.15	3
$15	$63.05	$14.09	0.22	$53.61	$11.94	0.22	–$9.43	–$2.15	4
$16	$67.05	$14.09	0.21	$53.61	$11.94	0.22	–$13.43	–$2.15	6
$17	$71.05	$14.09	0.20	$53.61	$11.94	0.22	–$17.43	–$2.15	8
$18	$75.05	$14.09	0.19	$53.61	$11.94	0.22	–$21.43	–$2.15	10
$19	$79.05	$14.09	0.18	$53.61	$11.94	0.22	–$25.43	–$2.15	12
$20	$83.05	$14.09	0.17	$53.61	$11.94	0.22	–$29.43	–$2.15	14
$21	$87.04	$14.09	0.16	$53.61	$11.94	0.22	–$33.43	–$2.15	16
$22	$91.04	$14.09	0.15	$53.61	$11.94	0.22	–$37.43	–$2.15	17
$23	$95.04	$14.09	0.15	$53.61	$11.94	0.22	–$41.43	–$2.15	19

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for antigen test cost was C_Ag. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 15. One-way sensitivity analysis of cost for clinical PCR tests in an economic evaluation of wastewater surveillance combined with clinical COVID-19 screening tests, Japan*

Clinical PCR test cost	Option 1†			Option 2†			Relative value of option 2		
	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
$20	$65.60	$14.08	0.215	$49.75	$11.94	0.24	–$15.85	–$2.15	7
$23	$65.86	$14.09	0.214	$50.46	$11.94	0.24	–$15.41	–$2.15	7
$27	$66.13	$14.09	0.213	$51.16	$11.94	0.23	–$14.97	–$2.15	7
$30	$66.40	$14.09	0.212	$51.87	$11.94	0.23	–$14.52	–$2.15	7
$33	$66.66	$14.09	0.211	$52.58	$11.94	0.23	–$14.08	–$2.15	7
$37	$66.93	$14.09	0.211	$53.29	$11.94	0.22	–$13.64	–$2.15	6

Clinical PCR test cost	Option 1†			Option 2†			Relative value of option 2		
	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
$40	$67.19	$14.09	0.210	$54.00	$11.94	0.22	–$13.19	–$2.15	6
$43	$67.46	$14.09	0.209	$54.71	$11.94	0.22	–$12.75	–$2.15	6
$46	$67.72	$14.09	0.208	$55.42	$11.94	0.22	–$12.30	–$2.15	6
$50	$67.99	$14.09	0.207	$56.13	$11.94	0.21	–$11.86	–$2.15	6
$53	$68.25	$14.10	0.207	$56.84	$11.94	0.21	–$11.42	–$2.15	5

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for clinical PCR test cost was C_PCR. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 16. One-way sensitivity analysis of cost for isolation per case in an economic evaluation of wastewater surveillance combined with clinical COVID-19 screening tests, Japan*

	Option 1†			Option 2†			Relative value of option 2		
Isolation cost	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
$379	$67.05	$14.03	0.209	$53.61	$11.90	0.222	–$13.43	–$2.12	6.33
$455	$67.05	$14.04	0.209	$53.61	$11.91	0.222	–$13.43	–$2.13	6.31
$530	$67.05	$14.05	0.210	$53.61	$11.92	0.222	–$13.43	–$2.13	6.30
$606	$67.05	$14.06	0.210	$53.61	$11.93	0.222	–$13.43	–$2.14	6.28
$682	$67.05	$14.08	0.210	$53.61	$11.93	0.223	–$13.43	–$2.14	6.26
$758	$67.05	$14.09	0.210	$53.61	$11.94	0.223	–$13.43	–$2.15	6.25
$833	$67.05	$14.10	0.210	$53.61	$11.95	0.223	–$13.43	–$2.16	6.23
$909	$67.05	$14.12	0.211	$53.61	$11.95	0.223	–$13.43	–$2.16	6.21
$985	$67.05	$14.13	0.211	$53.61	$11.96	0.223	–$13.43	–$2.17	6.20
$1,061	$67.05	$14.14	0.211	$53.61	$11.97	0.223	–$13.43	–$2.17	6.18
$1,136	$67.05	$14.15	0.211	$53.61	$11.98	0.223	–$13.43	–$2.18	6.17
$1,212	$67.05	$14.17	0.211	$53.61	$11.98	0.224	–$13.43	–$2.18	6.15
$1,288	$67.05	$14.18	0.212	$53.61	$11.99	0.224	–$13.43	–$2.19	6.13
$1,364	$67.05	$14.19	0.212	$53.61	$12.00	0.224	–$13.43	–$2.20	6.12
$1,439	$67.05	$14.21	0.212	$53.61	$12.01	0.224	–$13.43	–$2.20	6.10
$1,515	$67.05	$14.22	0.212	$53.61	$12.01	0.224	–$13.43	–$2.21	6.09

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for cost for isolation was C_isolation. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 17. One-way sensitivity analysis of hospitalization cost per case in an economic evaluation of wastewater surveillance combined with clinical COVID-19 screening tests, Japan*

Hospitalization cost	Option 1†			Option 2†			Relative value of option 2		
	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
$16,212	$67.05	$12.30	0.18	$53.61	$10.42	0.19	–$13.43	–$1.88	7
$16,856	$67.05	$12.66	0.19	$53.61	$10.72	0.20	–$13.43	–$1.94	7
$17,500	$67.05	$13.02	0.19	$53.61	$11.03	0.21	–$13.43	–$1.99	7
$18,144	$67.05	$13.38	0.20	$53.61	$11.33	0.21	–$13.43	–$2.04	7
$18,788	$67.05	$13.73	0.20	$53.61	$11.64	0.22	–$13.43	–$2.10	6
$19,432	$67.05	$14.09	0.21	$53.61	$11.94	0.22	–$13.43	–$2.15	6
$20,076	$67.05	$14.45	0.22	$53.61	$12.24	0.23	–$13.43	–$2.20	6
$20,720	$67.05	$14.80	0.22	$53.61	$12.55	0.23	–$13.43	–$2.26	6
$21,363	$67.05	$15.16	0.23	$53.61	$12.85	0.24	–$13.43	–$2.31	6
$22,007	$67.05	$15.52	0.23	$53.61	$13.15	0.25	–$13.43	–$2.36	6
$22,651	$67.05	$15.88	0.24	$53.61	$13.46	0.25	–$13.43	–$2.42	6
$23,295	$67.05	$16.23	0.24	$53.61	$13.76	0.26	–$13.43	–$2.47	5
$23,939	$67.05	$16.59	0.25	$53.61	$14.07	0.26	–$13.43	–$2.52	5
$24,583	$67.05	$16.95	0.25	$53.61	$14.37	0.27	–$13.43	–$2.58	5
$25,227	$67.05	$17.31	0.26	$53.61	$14.67	0.27	–$13.43	–$2.63	5

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for cost for hospitalization was C_hosp_all. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 18. One-way sensitivity analysis of COVID-19 incidence per million population in an economic evaluation of wastewater surveillance combined with clinical screening tests, Japan*

	Option 1†			Option 2†			Relative value of option 2		
Incidence	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
10	$67.04	$1.39	0.02	$53.60	$1.14	0.02	–$13.44	–$0.25	54
50	$67.04	$7.03	0.10	$53.61	$5.94	0.11	–$13.44	–$1.09	12
100	$67.05	$14.09	0.21	$53.61	$11.94	0.22	–$13.43	–$2.15	6
400	$67.07	$56.43	0.84	$53.66	$47.94	0.89	–$13.41	–$8.49	1.58
445	$67.08	$62.78	0.94	$53.67	$53.34	0.99	–$13.41	–$9.44	1.42
450	$67.08	$63.49	0.95	$53.67	$53.94	1.01	–$13.41	–$9.54	1.40
475	$67.08	$67.01	0.999	$53.67	$56.94	1.06	–$13.41	–$10.07	1.33
480	$67.08	$67.72	1.010	$53.67	$57.54	1.07	–$13.41	–$10.18	1.32
500	$67.08	$70.54	1.05	$53.68	$59.94	1.12	–$13.40	–$10.60	1.26
600	$67.09	$84.65	1.26	$53.69	$71.94	1.34	–$13.40	–$12.71	1.05
630	$67.09	$88.89	1.32	$53.70	$75.54	1.41	–$13.39	–$13.35	1.004
635	$67.09	$89.59	1.34	$53.70	$76.14	1.42	–$13.39	–$13.45	0.996
700	$67.10	$98.77	1.47	$53.71	$83.94	1.56	–$13.39	–$14.83	0.90
1,000	$67.12	$141.11	2	$53.75	$119.94	2	–$13.37	–$21.16	0.63
2,000	$67.20	$282.23	4	$53.91	$239.95	4	–$13.29	–$42.29	0.31
5,000	$67.45	$705.62	10	$54.37	$599.96	11	–$13.07	–$105.66	0.12
10,000	$67.85	$1,411.26	21	$55.14	$1,199.97	22	–$12.71	–$211.29	0.06

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for incidence was inc_n_per_M. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 19. One-way sensitivity analysis of number of residents at a facility in an economic evaluation of wastewater surveillance combined with COVID-19 clinical screening tests, Japan*

No. residents at a facility	Option 1†			Option 2†			Relative value of option 2		
	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
50	$67.05	$14.09	0.21	$99.06	$11.94	0.12	$32.02	–$2.15	−14.89
60	$67.05	$14.09	0.21	$83.91	$11.94	0.14	$16.87	–$2.15	−7.84
70	$67.05	$14.09	0.21	$73.09	$11.94	0.16	$6.05	–$2.15	−2.81
80	$67.05	$14.09	0.21	$64.98	$11.94	0.18	–$2.07	–$2.15	0.96
81	$67.05	$14.09	0.21	$64.28	$11.94	0.19	–$2.77	–$2.15	1.29
90	$67.05	$14.09	0.21	$58.66	$11.94	0.20	–$8.38	–$2.15	4
100	$67.05	$14.09	0.21	$53.61	$11.94	0.22	–$13.43	–$2.15	6
200	$67.05	$14.09	0.21	$30.89	$11.94	0.39	–$36.16	–$2.15	17
300	$67.05	$14.09	0.21	$23.31	$11.94	0.51	–$43.73	–$2.15	20
400	$67.05	$14.09	0.21	$19.53	$11.94	0.61	–$47.52	–$2.15	22
500	$67.05	$14.09	0.21	$17.25	$11.94	0.69	–$49.79	–$2.15	23
600	$67.05	$14.09	0.21	$15.74	$11.94	0.76	–$51.31	–$2.15	24
700	$67.05	$14.09	0.21	$14.66	$11.94	0.81	–$52.39	–$2.15	24
800	$67.05	$14.09	0.21	$13.85	$11.94	0.86	–$53.20	–$2.15	25
900	$67.05	$14.09	0.21	$13.21	$11.94	0.90	–$53.83	–$2.15	25
1,000	$67.05	$14.09	0.21	$12.71	$11.94	0.94	–$54.34	–$2.15	25

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for number of residents was N_facility_size. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 20. One-way sensitivity analysis of mortality rate among persons who tested COVID-19 positive in an economic evaluation of wastewater surveillance combined with clinical screening tests, Japan*

	Option 1†			Option 2†			Relative value of option 2		
Mortality rate	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
0.0018	$67.05	$12.55	0.19	$53.61	$10.63	0.20	–$13.43	–$1.92	7
0.002	$67.05	$12.73	0.19	$53.61	$10.79	0.20	–$13.43	–$1.95	7
0.003	$67.05	$13.64	0.20	$53.61	$11.56	0.22	–$13.43	–$2.08	6
0.004	$67.05	$14.54	0.22	$53.61	$12.32	0.23	–$13.43	–$2.22	6
0.005	$67.05	$15.45	0.23	$53.61	$13.09	0.24	–$13.43	–$2.35	6
0.006	$67.05	$16.35	0.24	$53.61	$13.86	0.26	–$13.43	–$2.49	5
0.007	$67.05	$17.26	0.26	$53.61	$14.63	0.27	–$13.43	–$2.62	5
0.008	$67.05	$18.16	0.27	$53.61	$15.40	0.29	–$13.43	–$2.76	5
0.009	$67.05	$19.07	0.28	$53.61	$16.17	0.30	–$13.43	–$2.90	5
0.0104	$67.05	$20.33	0.30	$53.61	$17.25	0.32	–$13.43	–$3.09	4

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for the mortality rate was r_mortality_test_positive. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 21. One-way sensitivity analysis of the ratio of mortality rates among persons ≥80 years of age compared with the general population in an economic evaluation of wastewater surveillance combined with COVID-19 clinical screening tests, Japan*

	Option 1†			Option 2†			Relative value of option 2		
Ratio	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
0.5	$67.05	$0.28	0.004	$53.61	$0.20	0.004	–$13.43	–$0.08	161
0.6	$67.05	$0.36	0.005	$53.61	$0.26	0.005	–$13.43	–$0.09	142
0.7	$67.05	$0.43	0.006	$53.61	$0.33	0.006	–$13.43	–$0.11	127
0.8	$67.05	$0.51	0.008	$53.61	$0.39	0.007	–$13.43	–$0.12	115
0.9	$67.05	$0.58	0.009	$53.61	$0.45	0.008	–$13.43	–$0.13	105
1	$67.05	$0.66	0.010	$53.61	$0.52	0.010	–$13.43	–$0.14	96
1.1	$67.05	$0.73	0.011	$53.61	$0.58	0.011	–$13.43	–$0.15	89
1.2	$67.05	$0.80	0.012	$53.61	$0.64	0.012	–$13.43	–$0.16	83
1.3	$67.05	$0.88	0.013	$53.61	$0.71	0.013	–$13.43	–$0.17	78
1.4	$67.05	$0.95	0.014	$53.61	$0.77	0.014	–$13.43	–$0.18	73
1.5	$67.05	$1.03	0.02	$53.61	$0.83	0.02	–$13.43	–$0.20	69
15	$67.05	$11.10	0.17	$53.61	$9.40	0.18	–$13.43	–$1.70	8
16	$67.05	$11.85	0.18	$53.61	$10.04	0.19	–$13.43	–$1.82	7
17	$67.05	$12.60	0.19	$53.61	$10.67	0.20	–$13.43	–$1.93	7
18	$67.05	$13.34	0.20	$53.61	$11.31	0.21	–$13.43	–$2.04	7
19	$67.05	$14.09	0.21	$53.61	$11.94	0.22	–$13.43	–$2.15	6
20	$67.05	$14.84	0.22	$53.61	$12.57	0.23	–$13.43	–$2.26	6
21	$67.05	$15.58	0.23	$53.61	$13.21	0.25	–$13.43	–$2.37	6
22	$67.05	$16.33	0.24	$53.61	$13.84	0.26	–$13.43	–$2.49	5

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for the ratio of mortality rates among persons ≥80 years of age compared with persons <80 years of age was V_mr_ratio. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 22. One-way sensitivity analysis of life years saved due to avoiding COVID-19 infection in an economic evaluation of wastewater surveillance combined with COVID-19 clinical screening tests, Japan*

	Option 1†			Option 2†			Relative value of option 2		
Years saved	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
11.1	$67.05	$14.01	0.209	$53.61	$11.87	0.221	–$13.43	–$2.14	6.28
11.2	$67.05	$14.03	0.209	$53.61	$11.89	0.222	–$13.43	–$2.14	6.27
11.3	$67.05	$14.06	0.210	$53.61	$11.92	0.222	–$13.43	–$2.15	6.26
11.4	$67.05	$14.09	0.210	$53.61	$11.94	0.223	–$13.43	–$2.15	6.25
11.5	$67.05	$14.12	0.211	$53.61	$11.96	0.223	–$13.43	–$2.15	6.23
11.6	$67.05	$14.15	0.211	$53.61	$11.99	0.224	–$13.43	–$2.16	6.22
11.7	$67.05	$14.17	0.211	$53.61	$12.01	0.224	–$13.43	–$2.16	6.21

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for life years saved was V_life_yrs_saved. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 23. One-way sensitivity analysis of the ratio to convert life-years saved to quality adjusted life years (QALYs) saved in an economic evaluation of wastewater surveillance combined with COVID-19 clinical screening tests, Japan*

	Option 1†			Option 2†			Relative value of option 2		
Ratio	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
0.64	$67.05	$13.90	0.207	$53.61	$11.78	0.220	–$13.43	–$2.12	6.33
0.65	$67.05	$13.95	0.208	$53.61	$11.82	0.220	–$13.43	–$2.13	6.31
0.66	$67.05	$14.00	0.209	$53.61	$11.86	0.221	–$13.43	–$2.14	6.29
0.67	$67.05	$14.04	0.209	$53.61	$11.90	0.222	–$13.43	–$2.14	6.27
0.68	$67.05	$14.09	0.210	$53.61	$11.94	0.223	–$13.43	–$2.15	6.25
0.69	$67.05	$14.14	0.211	$53.61	$11.98	0.223	–$13.43	–$2.16	6.23
0.7	$67.05	$14.18	0.212	$53.61	$12.02	0.224	–$13.43	–$2.16	6.21
0.71	$67.05	$14.23	0.212	$53.61	$12.06	0.225	–$13.43	–$2.17	6.19

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for the ratio to convert life-years saved to quality adjusted life years was r_QALY_adj. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 24. One-way sensitivity analysis of hospitalization rates among persons who tested COVID-19 positive in an economic evaluation of wastewater surveillance combined with COVID-19 clinical screening tests, Japan*

	Option 1†			Option 2†			Relative value of option 2		
Rate	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
0.04	$67.05	$5.41	0.08	$53.61	$4.46	0.08	–$13.43	–$0.95	14
0.06	$67.05	$6.63	0.10	$53.61	$5.50	0.10	–$13.43	–$1.14	12
0.08	$67.05	$7.86	0.12	$53.61	$6.54	0.12	–$13.43	–$1.32	10
0.1	$67.05	$9.09	0.14	$53.61	$7.60	0.14	–$13.43	–$1.49	9
0.12	$67.05	$10.33	0.15	$53.61	$8.67	0.16	–$13.43	–$1.66	8
0.14	$67.05	$11.58	0.17	$53.61	$9.75	0.18	–$13.43	–$1.83	7
0.16	$67.05	$12.83	0.19	$53.61	$10.84	0.20	–$13.43	–$1.99	7
0.18	$67.05	$14.09	0.21	$53.61	$11.94	0.22	–$13.43	–$2.15	6
0.2	$67.05	$15.35	0.23	$53.61	$13.05	0.24	–$13.43	–$2.30	6
0.22	$67.05	$16.62	0.25	$53.61	$14.17	0.26	–$13.43	–$2.45	5
0.24	$67.05	$17.89	0.27	$53.61	$15.29	0.29	–$13.43	–$2.60	5
0.26	$67.05	$19.17	0.29	$53.61	$16.43	0.31	–$13.43	–$2.74	5
0.28	$67.05	$20.45	0.31	$53.61	$17.57	0.33	–$13.43	–$2.88	5
0.3	$67.05	$21.74	0.32	$53.61	$18.72	0.35	–$13.43	–$3.02	4
0.32	$67.05	$23.03	0.34	$53.61	$19.88	0.37	–$13.43	–$3.15	4
0.34	$67.05	$24.32	0.36	$53.61	$21.04	0.39	–$13.43	–$3.28	4
0.36	$67.05	$25.62	0.38	$53.61	$22.21	0.41	–$13.43	–$3.41	4
0.38	$67.05	$26.92	0.40	$53.61	$23.39	0.44	–$13.43	–$3.53	4
0.40	$67.05	$28.23	0.42	$53.61	$24.57	0.46	–$13.43	–$3.66	4

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for the hospitalization rates among persons who tested COVID-19 positive was r_hosp_test_positive. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 25. One-way sensitivity analysis for the proportion of severe cases among hospitalized cases in an economic evaluation of wastewater surveillance combined with COVID-19 clinical screening tests, Japan*

	Option 1†			Option 2†			Relative value of option 2		
Proportion	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
0.05	$67.05	$12.28	0.18	$53.61	$10.38	0.19	–$13.43	–$1.90	7
0.06	$67.05	$12.64	0.19	$53.61	$10.69	0.20	–$13.43	–$1.95	7
0.07	$67.05	$13.00	0.19	$53.61	$11.00	0.21	–$13.43	–$2.00	7
0.08	$67.05	$13.37	0.20	$53.61	$11.31	0.21	–$13.43	–$2.05	7
0.09	$67.05	$13.73	0.20	$53.61	$11.63	0.22	–$13.43	–$2.10	6
0.1	$67.05	$14.09	0.21	$53.61	$11.94	0.22	–$13.43	–$2.15	6
0.11	$67.05	$14.45	0.22	$53.61	$12.25	0.23	–$13.43	–$2.20	6
0.12	$67.05	$14.82	0.22	$53.61	$12.57	0.23	–$13.43	–$2.25	6
0.13	$67.05	$15.18	0.23	$53.61	$12.88	0.24	–$13.43	–$2.30	6
0.14	$67.05	$15.54	0.23	$53.61	$13.20	0.25	–$13.43	–$2.35	6
0.15	$67.05	$15.91	0.24	$53.61	$13.51	0.25	–$13.43	–$2.40	6
0.16	$67.05	$16.27	0.24	$53.61	$13.83	0.26	–$13.43	–$2.44	5
0.17	$67.05	$16.64	0.25	$53.61	$14.14	0.26	–$13.43	–$2.49	5
0.18	$67.05	$17.00	0.25	$53.61	$14.46	0.27	–$13.43	–$2.54	5
0.19	$67.05	$17.36	0.26	$53.61	$14.78	0.28	–$13.43	–$2.59	5

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for the proportion of severe cases was r_icu_hosp. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 26. One-way sensitivity analysis of effective reproduction number (R_e) in an economic evaluation of wastewater surveillance combined with COVID-19 clinical screening tests, Japan*

	Option 1†			Option 2†			Relative value of option 2		
R_e	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
0.9	$67.05	$18.63	0.28	$53.62	$16.70	0.31	–$13.43	–$1.93	7

	Option 1†			Option 2†			Relative value of option 2		
R_e	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
1	$67.05	$17.02	0.25	$53.62	$15.05	0.28	–$13.43	–$1.97	7
1.1	$67.05	$15.80	0.24	$53.62	$13.78	0.26	–$13.43	–$2.02	7
1.2	$67.05	$14.85	0.22	$53.62	$12.77	0.24	–$13.43	–$2.08	6
1.3	$67.05	$14.09	0.21	$53.61	$11.94	0.22	–$13.43	–$2.15	6
1.4	$67.05	$13.48	0.20	$53.61	$11.25	0.21	–$13.43	–$2.23	6
1.5	$67.05	$12.98	0.19	$53.61	$10.66	0.20	–$13.43	–$2.32	6
1.6	$67.05	$12.56	0.19	$53.61	$10.15	0.19	–$13.43	–$2.41	6
1.7	$67.05	$12.21	0.18	$53.61	$9.70	0.18	–$13.43	–$2.51	5
1.8	$67.05	$11.92	0.18	$53.61	$9.30	0.17	–$13.44	–$2.62	5
1.9	$67.05	$11.66	0.17	$53.61	$8.93	0.17	–$13.44	–$2.73	5
2.0	$67.05	$11.44	0.17	$53.61	$8.60	0.16	–$13.44	–$2.84	5

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for effective reproduction number was R_e. Gray shading indicates ROI >1. Inc., incremental; R_e, effective reproduction number; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option’s ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2’s relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2’s relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 27. One-way sensitivity analysis of effectiveness of screening in reducing hospitalization and mortality rates because of an earlier COVID-19 diagnosis in an economic evaluation of wastewater surveillance combined with clinical screening tests, Japan*

	Option 1†			Option 2†			Relative value of option 2		
Effectiveness	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
0.23	$67.05	$6.08	0.09	$53.61	$5.13	0.10	–$13.43	–$0.95	14
0.25	$67.05	$6.60	0.10	$53.61	$5.57	0.10	–$13.43	–$1.03	13
0.3	$67.05	$7.89	0.12	$53.61	$6.67	0.12	–$13.43	–$1.22	11
0.35	$67.05	$9.18	0.14	$53.61	$7.77	0.14	–$13.43	–$1.42	9
0.4	$67.05	$10.47	0.16	$53.61	$8.87	0.17	–$13.43	–$1.61	8
0.45	$67.05	$11.77	0.18	$53.61	$9.96	0.19	–$13.43	–$1.80	7
0.5	$67.05	$13.06	0.19	$53.61	$11.06	0.21	–$13.43	–$2.00	7
0.55	$67.05	$14.35	0.21	$53.61	$12.16	0.23	–$13.43	–$2.19	6
0.6	$67.05	$15.64	0.23	$53.61	$13.26	0.25	–$13.43	–$2.38	6
0.62	$67.05	$16.16	0.24	$53.61	$13.70	0.26	–$13.43	–$2.46	5

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for effectiveness of early diagnosis was Eff_early_Dx. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

Appendix Table 28. One-way sensitivity analysis of the ratio of the loss value of missing an infected case compared with the benefit value of finding an infected case in an economic evaluation of wastewater surveillance combined with COVID-19 clinical screening tests, Japan*

Ratio of	Option 1†			Option 2†			Relative value of option 2		
loss value	Cost	Benefit	ROI‡	Cost	Benefit	ROI‡	Inc. cost§	Inc. benefit¶	Rel. ROI#
0.0	$67.05	$16.74	0.25	$53.61	$16.65	0.31	–$13.43	–$0.09	148
0.1	$67.05	$16.48	0.25	$53.61	$16.18	0.30	–$13.43	–$0.30	45
0.2	$67.05	$16.21	0.24	$53.61	$15.71	0.29	–$13.43	–$0.50	27
0.3	$67.05	$15.95	0.24	$53.61	$15.24	0.28	–$13.43	–$0.71	19
0.4	$67.05	$15.68	0.23	$53.61	$14.77	0.28	–$13.43	–$0.91	15
0.5	$67.05	$15.42	0.23	$53.61	$14.30	0.27	–$13.43	–$1.12	12
0.6	$67.05	$15.15	0.23	$53.61	$13.82	0.26	–$13.43	–$1.33	10
0.7	$67.05	$14.89	0.22	$53.61	$13.35	0.25	–$13.43	–$1.53	9
0.8	$67.05	$14.62	0.22	$53.61	$12.88	0.24	–$13.43	–$1.74	8
0.9	$67.05	$14.36	0.21	$53.61	$12.41	0.23	–$13.43	–$1.94	7
1	$67.05	$14.09	0.21	$53.61	$11.94	0.22	–$13.43	–$2.15	6
1.1	$67.05	$13.83	0.21	$53.61	$11.47	0.21	–$13.43	–$2.36	6
1.2	$67.05	$13.56	0.20	$53.61	$11.00	0.21	–$13.43	–$2.56	5
1.3	$67.05	$13.29	0.20	$53.61	$10.53	0.20	–$13.43	–$2.77	5
1.4	$67.05	$13.03	0.19	$53.61	$10.06	0.19	–$13.43	–$2.97	5
1.5	$67.05	$12.76	0.19	$53.61	$9.58	0.18	–$13.43	–$3.18	4
1.6	$67.05	$12.50	0.19	$53.61	$9.11	0.17	–$13.43	–$3.39	4
1.7	$67.05	$12.23	0.18	$53.61	$8.64	0.16	–$13.43	–$3.59	4
1.8	$67.05	$11.97	0.18	$53.61	$8.17	0.15	–$13.43	–$3.80	4
1.9	$67.05	$11.70	0.17	$53.61	$7.70	0.14	–$13.43	–$4.00	3
2.0	$67.05	$11.44	0.17	$53.61	$7.23	0.13	–$13.43	–$4.21	3

*Cost reported in USD; the exchange rate of ¥132 per $1 USD was used as the annual average in 2022 based on the report by the Bank of Japan (*4*). The model input for the ratio of the loss value was r_B_Loss. Gray shading indicates ROI >1. Inc., incremental; Rel., relative.

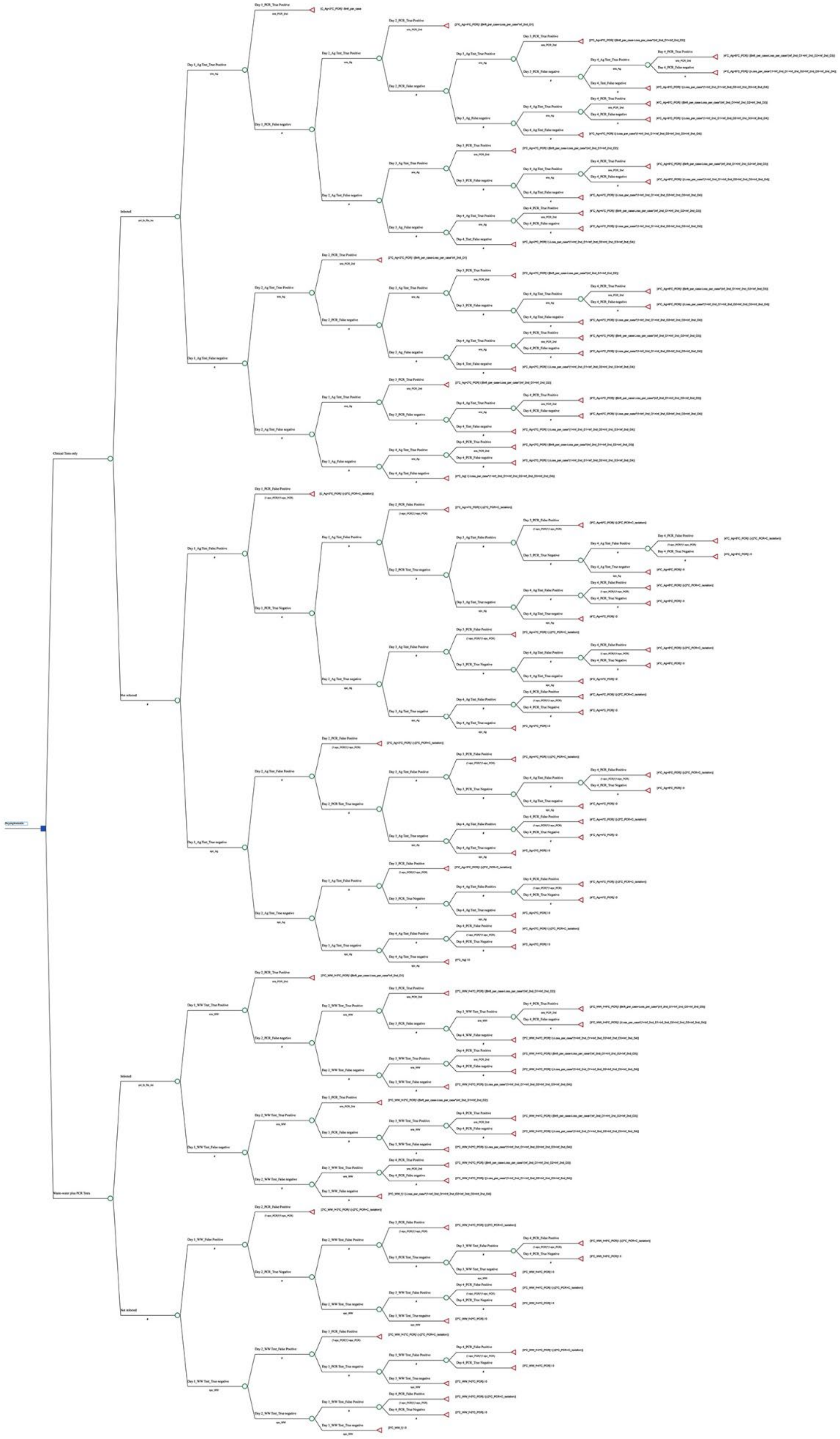
†Option 1 is clinical tests only; option 2 is wastewater surveillance and clinical tests. Inc., incremental; ROI, return on investment. If an option is cost-saving compared with its comparator, the option's ROI is estimated to exceed 1. The comparator of options 1 and 2 is do-nothing.

‡ROI is benefit divided by cost for each option.

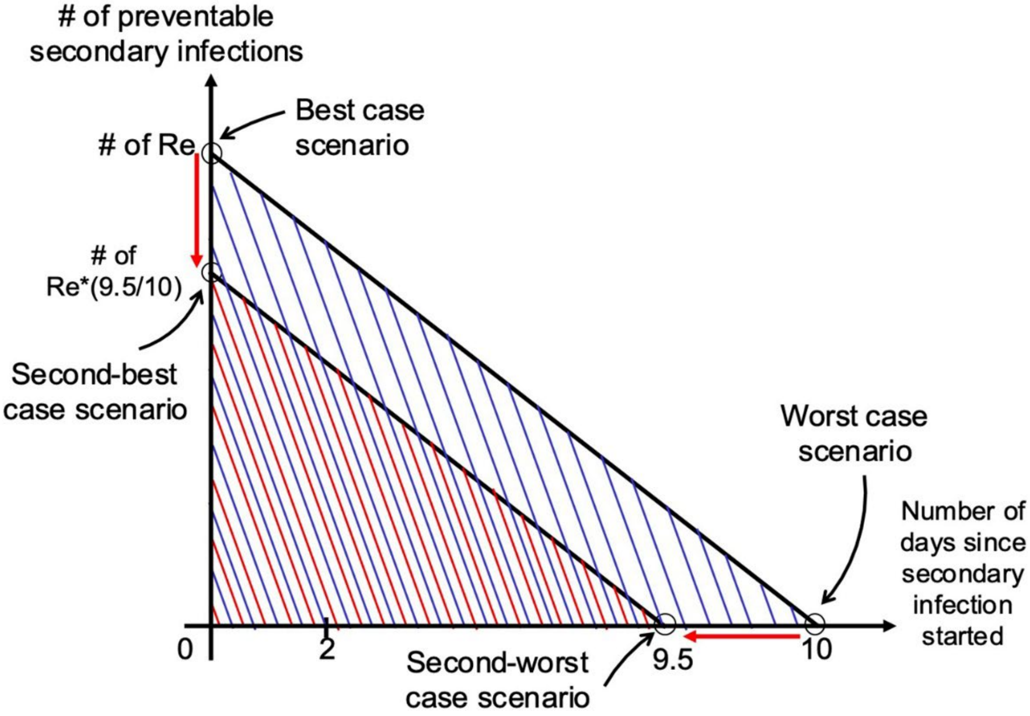
§Incremental cost is the cost of option 2 minus cost of option 1. A negative value of incremental cost indicates that option 2 has a lower cost or is cost-saving, compared with option 1. This could be interpreted as option 2's relative benefit.

¶Incremental benefit is the benefit of option 2 minus benefit of option 1. A negative value of incremental benefit indicates that option 2 has a lower benefit compared with option 1, which could be interpreted as option 2's relative cost.

#Relative ROI is incremental cost divided by incremental benefit.

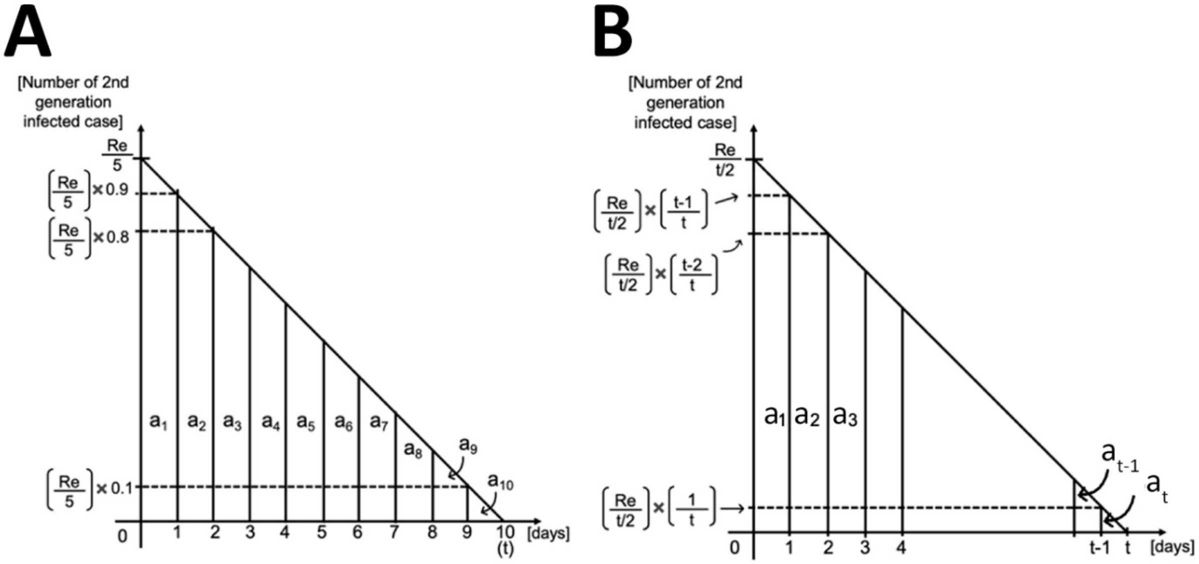

Asymptomatic
Clinical Tests only
Infected
Day 1_Ag Test_True Positive
Day 1_PCR_True Positive
Day 1_PCR_False negative
Day 2_Ag Test_True Positive
Day 2_Ag Test_False negative
Day 2_PCR_True Positive
Day 2_PCR_False negative
Not infected
Day 1_Ag Test_False Positive
Day 1_Ag Test_True negative
Waste water plus PCR Tests

Appendix Figure 1. Decision tree used in an economic evaluation of wastewater surveillance combined with COVID-19 clinical screening tests, Japan. A blue square indicates a choice facing the decision maker. Green circles indicate an event that has multiple possible outcomes and is not under the decision maker's control; red triangles indicate the endpoint of a scenario. Bnft_per_case, benefit of finding one infected case by a screening; Loss_per_case, value of missing one infected case; C_Ag, antigen test cost; C_hosp_all, hospitalization cost per case; C_isolation, isolation cost for a test-positive; C_PCR, clinical PCR test cost; C_ww_f, labor cost (to sample at a facility) plus laboratory cost of wastewater surveillance per day per facility; Inf_2nd_D1, the number of newly produced second-generation infected cases on Day 1; Inf_2nd_D2, the number of newly produced second-generation infected cases on Day 2; Inf_2nd_D3, the number of newly produced second-generation infected cases on Day 3; Inf_2nd_D4, the number of newly produced second-generation infected cases on Day 4; sns_Ag, sensitivity of antigen test; sns_PCR_2nd, sensitivity of clinical PCR test subsequent to a positive test of antigen test; sns_WW, sensitivity of wastewater surveillance; spc_Ag, specificity of antigen test; spc_PCR, specificity of clinical PCR test.

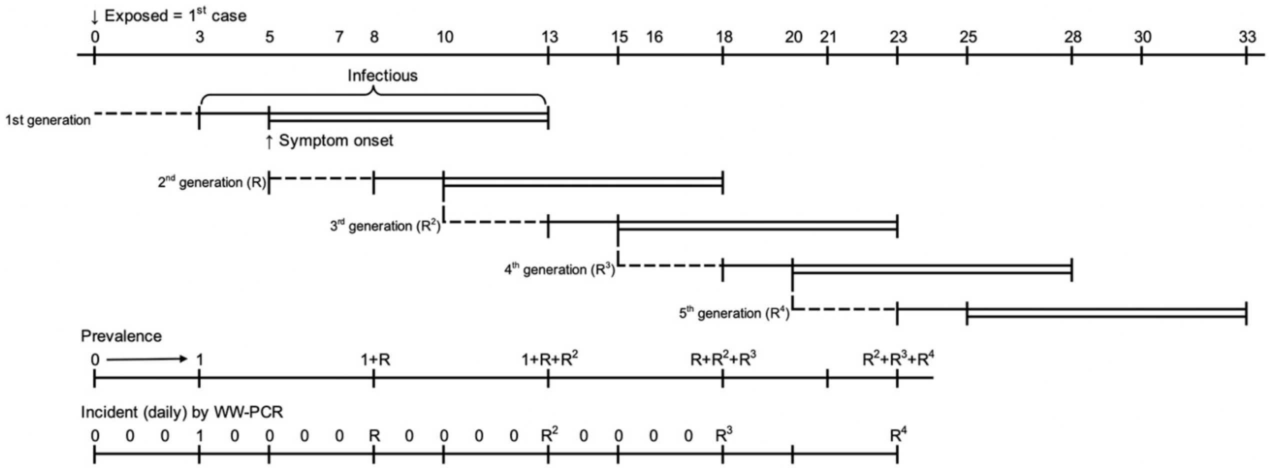


Note: Re represents reproduction number.

Appendix Figure 2. Number of preventable secondary infections assumed in an economic evaluation of wastewater surveillance combined with COVID-19 clinical screening tests, Japan. Y-axis indicates the number of preventable secondary infections for each day during an infectious period, which is indicated by x-axis. Blue striped (lighter shadow in black and white) area indicates the probabilistic summed number of the preventable secondary infections based on the less realistic best-case and worst-case scenarios explained in the text. Red and blue striped (darker shadow in black and white) area indicates the probabilistic summed number of the preventable secondary infections based on the more realistic second-best-case and second-worst-case scenarios.



Appendix Figure 3. Number of second-generation infected cases yielded by a missed first-generation infected case in an economic evaluation of wastewater surveillance combined with COVID-19 clinical screening tests, Japan. A) Assumed 10-day infectious period; B) Infectious period is expressed as t, and was assigned a triangular distribution. A trapezoid area "a_i" indicates the number of second-generation infected cases yielded by a missed first-generation infected case for day "i" during an infectious period, which is indicated by X-axis. Only for the final day of the infectious period, a far-right triangular area (a_{10} in A and a_t in B) indicates the number of second-generation infected cases yielded by a missed first-generation infected case; R_e, effective reproduction number; t, time in days during an infectious period.



Appendix Figure 4. Relationship between prevalence and incidence in an economic evaluation of wastewater surveillance combined with COVID-19 clinical screening tests, Japan. The timeline demonstrates time in days from the first case being infected over several generations. Each subsequent generation is assumed to be produced only on the symptom onset day of a previous generation for simplicity. The bottom 2 lines indicate prevalence and daily incidence. A part of daily incidence (newly infected cases) is detected by wastewater surveillance (WW) or antigen tests, subsequently confirmed by clinical PCR tests.