

# Modeling Donor Screening Strategies to Reduce the Risk of Severe Acute Respiratory Syndrome Coronavirus 2 Transmission via Fecal Microbiota Transplantation

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The potential for transmission of severe acute respiratory syndrome coronavirus 2 shed in stool via fecal microbiota transplantation is not yet known, and the effectiveness of various testing strategies to prevent fecal microbiota transplantation-based transmission has also not yet been quantified. In this study, we use a mathematical model to simulate the utility of different testing strategies.

**Keywords.** Clostridioides difficile; fecal microbiota transplantation; SARS-CoV-2.

Fecal microbiota transplantation (FMT), the instillation of stool from a healthy donor into a patient's gut, is a recommended therapy for the most common hospital-acquired infection in the United States, *Clostridioides difficile*, and is being explored as an experimental therapy for dozens of other conditions [1, 2]. As with all human-derived therapies, the safety of FMT depends on screening donors to prevent transmission of pathogens via the procedure [3], and screening guidelines must be continually updated to account for emerging pathogens [4].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), is primarily considered a respiratory pathogen, but evidence suggests that the virus is able to independently replicate in the gut, raising the possibility of transmission via the fecal-oral route or via FMT [5]. Practitioners [5–7] and regulators [8] have therefore called for screening of FMT donors for SARS-CoV-2. However, because of the virus's long incubation period, the high proportion of infected individuals that are asymptomatic [9], and the long period in which apparently recovered

individuals can continue to shed virus in their stool [10–13], screening FMT donors using COVID-19 clinical assessment alone may be insufficient, and the optimal available strategy for detecting asymptomatic carriage among FMT donors is unclear. Therefore, we developed a mathematical model of SARS-CoV-2 infection among FMT donors that simulates the effect of testing using polymerase chain reaction (PCR) with nasopharyngeal swabs, stool-based PCR tests, donor serology tests, or a combination of those assays. The model quantifies the effect of more stringent testing on the desirable reduction in potentially infectious, virus-positive donations processed into FMT material and released for use as well as the undesirable reduction in virus-negative donations released.

## METHODS

### Model Overview

We built an abstract model of FMT donors, simulating their donation schedule, SARS-CoV-2 infection incidence, and COVID-19 disease course. We incorporated various screening strategies, accounting for the imperfect specificity and sensitivity of each test, to estimate how many virus-negative donations would be appropriately released for use and how many virus-positive donations would be undesirably released. A conceptual overview of the model is given here. A step-by-step algorithm is in the [Supplemental Information](#), and example simulations are shown in [Supplemental Data 1](#). Parameters for the model are in [Table 1](#).

### Modeled Disease Course

We simulate the course of SARS-CoV-2 infection according to the general model by Sethuraman et al [14]. A donor is either uninfected or in 1 of 4 disease phases, summarized in [Supplemental Table 1](#). Each donor has a daily probability of becoming infected. Once a donor is infected, they progress through 4 disease phases. (1) Infected  $I_1$  - Donors in this phase have detectable virus in the nasopharynx, but they do not shed virus in stool and do not have detectable immunoglobulin (Ig) G antibodies. They may be symptomatic. We ignore any latent period, because it is not relevant to the model: symptomatic donors display symptoms on their first day in this phase. (2) Infected  $I_2$  - Donors in this phase still have detectable virus in the nasopharynx but still do not have detectable antibodies. A proportion of  $I_2$  donors are “stool shedders.” Shedders have detectable virus in their stool, and donations produced by shedders are virus-positive. (3) Recovered  $R_1$  - These donors no longer carry detectable virus in their nasopharynx, but they still potentially shed virus in stool, and they now have detectable antibodies. (4) Fully recovered  $R_2$  - These donors do not have

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**Table 1. Parameter Values**

Parameter	Point Estimate	Lower Bound	Upper Bound	Source
Maximum simulation length (days)	365	—	—	Assumption <sup>a</sup>
Days between donations	4	1	10	Assumption <sup>a</sup>
Incidence (daily probability of infection)	10 <sup>-3</sup>	10 <sup>-4</sup>	10 <sup>-2</sup>	Assumption <sup>b</sup>
$I_1$ duration (days)	2	1	4	[11, 12, 16, 17]
$I_2$ duration (days)	5	3	10	[11, 12, 16, 17]
$R_1$ duration (days)	15	10	30	[11, 12, 16–19]
Probability that an infected donor is asymptomatic	0.40	0.10	0.70	[9]
Probability that an infected donor sheds virus in stool	0.50	0.33	0.66	[10, 13, 16, 17]
Days of donations rejected before development of symptoms	14	—	—	Assumption <sup>a</sup>
Days between serology tests	60	—	—	Assumption <sup>a</sup>
Serology test sensitivity	0.75	0.65	0.90	[20–22]
Serology test specificity	0.98	0.90	0.99	[21, 22]
Days between swab tests	14	—	—	Assumption <sup>a</sup>
Swab test sensitivity	0.75	0.50	0.98	[23, 24]
Swab test specificity	0.95	0.90	0.99	[24]
Stool test sensitivity	0.80	0.50	0.99	Assumption <sup>c</sup>
Stool test specificity	0.99	0.95	0.99	Assumption <sup>c</sup>

NOTES: See [Supplemental Table 1](#) for a summary of the meanings of the  $I_1$ ,  $I_2$ ,  $R_1$ , and  $R_2$  categories. The lower and upper bounds represent the bounds of uniform distributions used when drawing random parameter values in the sensitivity analysis.

<sup>a</sup>Informed by operations at a large stool bank [4].

<sup>b</sup>The point estimate of 10<sup>-3</sup> corresponds to 35 000 daily cases in a population of 350 million, approximating the US average in early April 2020.

<sup>c</sup>Informed by an assay being implemented at a large stool bank.

detectable virus in the nasopharynx or in stool, but they do have detectable antibodies. We did not consider the role of immunity because the chance of multiple asymptomatic, undetected infections during the simulation period is low.

### Modeled Screening Strategies

Simulated donors are screened for the virus according to a screening strategy that consists of 1 or more of 4 individual test types: (1) daily symptoms checks; (2) nasopharyngeal PCR swabs test performed at 14-day intervals; (3) blood IgG antibody tests at 60-day intervals; (4) stool PCR tests performed at 14-day intervals, at 28-day intervals, or at every donation.

In simulations, we evaluated the following 10 screening strategies: (1) no molecular tests (ie, symptoms checks only); (2) symptoms checks and stool testing at 28-day intervals; (3) symptoms checks and stool testing at 14-day intervals; (4) symptoms checks and testing every stool; (5) symptoms checks and nasopharyngeal swabs; (6) symptoms checks, nasopharyngeal swabs, and stool tests at 28-day intervals; (7) symptoms checks, nasopharyngeal swabs, and stool tests at 14-day intervals; (8) Symptoms checks, nasopharyngeal swabs, and stool tests on every donation; (9) symptoms checks, nasopharyngeal swabs, and serology; and (10) symptoms checks, nasopharyngeal swabs, serology, and stool tests on every donation.

Donations are either rejected (ie, destroyed) or released for clinical use depending on the results of the tests implemented in a testing strategy. A donation is released only if it eligible for release under all tests implemented in the testing strategy. If donor becomes symptomatic, only the donations from more

than 14 days before onset of symptoms are eligible for release. For swab, serology, and stool tests, donations are eligible for release according to a “bookend” system: donations are eligible for release only if they are “bookended” by 2 negative tests [4]. In other words, any donations made after the last negative test conducted before the first positive test are rejected.

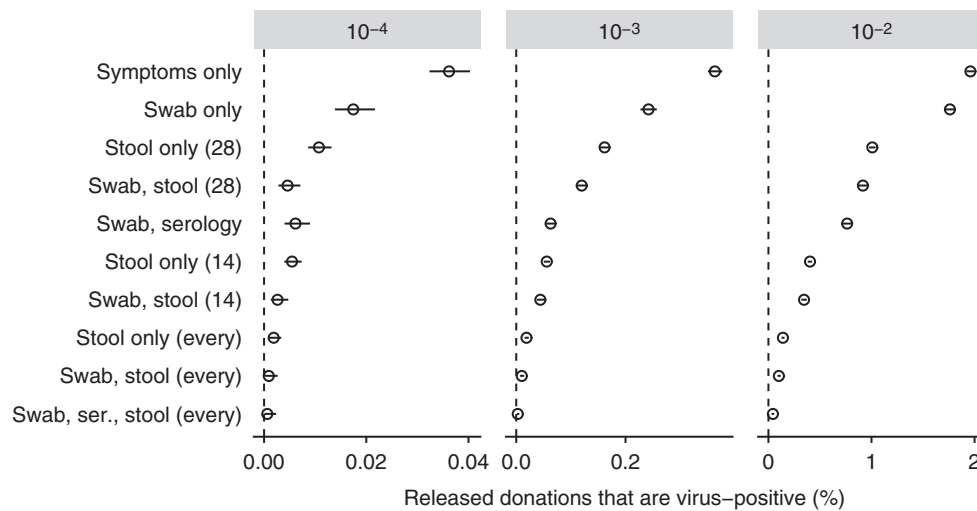
### Model Outcomes

The model has 2 outcomes: the number of “true negative,” virus-negative donations released and the number of “false negative,” virus-positive donations released. A desirable screening strategy will release many virus-negative donations and few or no virus-positive donations, whereas a poor strategy will needlessly destroy many virus-negative donations or release many virus-positive donations.

### Simulations and Analysis

To evaluate the effectiveness of different testing strategies, 10 000 simulations were run for each of 3 incidences (1 infection per 100 people per day; 1 per 1000; or 1 per 10 000) and each of the 10 screening strategies listed above.

To evaluate the sensitivity of the model outcomes to the input parameters, 10 000 simulations were run with varying parameters. All parameters were varied simultaneously. In each simulation, random values were drawn for each parameter from a uniform distribution whose lower and upper bounds are shown in [Table 1](#). Sensitivity between each input parameter and each of the 2 outcomes was assessed using Spearman’s  $\rho$  correlation.



**Figure 1.** Proportion of released donations that are virus positive (x-axis) in simulations at different daily incidences (insets, infections per person per day) using different testing strategies (y-axis). For a 10-fold decrease in incidence, approximately 10-fold fewer positive donations are released (N.B. different x-axis scales), but the relative ordering of the strategies remains similar. Swabs are always at 14-day intervals and serology is always at 60-day intervals. Stool tests are performed at 14-day intervals, 28-day intervals, or for every donation. All testing strategies include symptoms checks. Circles show point estimates; horizontal lines show 95% confidence intervals (binomial test).

Simulations and analyses were run using R (version 3.6.0) [15]. Code to reproduce the results is available online ([doi.org/10.5281/zenodo.3903840](https://doi.org/10.5281/zenodo.3903840)).

## RESULTS

The number of virus-positive and -negative donations released varied over simulations and depended on the incidence of infection and the testing strategy (Figure 1, Supplemental Table 2). As expected, the risk that a released donation is virus-positive varied approximately proportionally with the incidence of infection: a 10-fold increase in incidence led to an approximately 10-fold increase in risk. Also as expected, the more stringent strategies released fewer virus-positive donations, but they also released fewer virus-negative donations per donor due to false-positive test results (Supplemental Table 2). Thus, the more sensitive strategies were also less specific.

Testing strategies decreased the risk of a released donation being virus positive by similar factors regardless of the incidence of infection (Supplemental Figure 1, Supplemental Table 2). For example, whether the incidence of infection was 1 per 100 people per day or only 1 per 10 000, the odds that a released donation would be virus positive was 48- or 127-fold lower, respectively, under the most stringent strategy (symptoms checks, nasopharyngeal swabs, serology tests, and testing every stool) compared with symptoms checks alone. In a sensitivity analysis (Supplemental Figure 2), the parameters most strongly associated with the 2 outcomes (Spearman's  $\rho > 10\%$ ) were SARS-CoV-2 incidence, donation interval, the specificities of the stool and swab tests, and the probability of asymptomatic infection.

## DISCUSSION

A mathematical model of SARS-CoV-2 infection among stool donors suggests that, if the parameter estimates are accurate and a stringent testing strategy is used, then the probability of releasing a virus-positive donation for clinical use is low. More stringent tests were more sensitive but also less specific, and the most appropriate strategy must be determined by a balance between the necessary stringency and logistical considerations such as resourcing.

The strength of this analysis is its quantitative treatment of a pressing clinical question. However, it has multiple limitations. First, as a modeling study, the accuracy of the results depends on the accuracy of the input parameters and the appropriateness of the model structure, especially the tests' sensitivity and specificity, which remain subject to refinement, as well as the incidence of SARS-CoV-2 infection, which may differ between stool donors compared with the general population. Thus, the quantitative predictions made by the model should be used as a guide for evaluating the costs and benefits of more stringent testing rather than as a direct calculation of the risk of FMT material being virus positive. Second, the model makes a number of assumptions about the course of disease that may be shown to be invalid or that are no longer applicable. For example, our assumption that newly enrolled donors are seronegative maximizes the sensitivity of serology testing. As the number of candidate donors with positive serology rises, the sensitivity and utility of the serology test will decline. Finally, verifying the model would be challenging, because the possibility of fecal-oral transmission of SARS-CoV-2 has not been confirmed, and there is no accepted "gold standard" for detecting SARS-CoV-2 in stool.

## CONCLUSIONS

Although these results are encouraging, we again caution that they depend on several assumptions about testing quality, available testing modalities, and SARS-CoV-2 epidemiology that will be refined in the coming months. Nevertheless, this method is valuable in assessing the risks of transmission in this evolving pandemic, and we hope this approach can serve as a model for evaluating testing strategies for other pathogens or human-derived therapies beyond FMT.

## Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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