Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.
eAppendix. Agent-Based Simulation Model

Our agent-based model simulates *C. difficile* transmission in a 200-bed adult inpatient hospital. Full model details including parameter estimation, calibration, verification, and validation are provided in a prior publication, from which this is adapted.² The model represents a general US hospital, however it could be adapted to represent any specific real-world institution. To maximize generalizability, model input and intervention parameters were derived from over 100 peer-reviewed studies, published through April 2017 (selected parameters included in Table 1). The modeled hospital is comprised of 10 identical wards (eFigure 1), each of which contains 20 single-bed patient rooms, a nursing station, physician workroom, and common room for visitors and patients. Each model run includes a 28-day warmup period, followed by one simulated year of data collection. Among other measures, the model outputs the annual number of hospital-onset *C. difficile* infections (HO-CDI), defined as symptomatic diarrhea plus a positive laboratory test result on a specimen collected more than three days after hospital admission.³ The cost per HO-CDI averted and cost per quality-adjusted life year (QALY) saved are the two primary outcomes of the cost-effectiveness study. The model has four different types of agents as described below.

Patients: Upon arrival to the hospital, patients are assigned a specific ward and room number. Each patient is also assigned an initial clinical state, which is subsequently updated every 6 hours based on probabilities in the model’s discrete-time Markov chain. This discrete-time Markov chain was selected after extensive calibration from a subset of ten transition matrices run on the model simultaneously to account for population heterogeneity, as described by Barker, et al.² and Codella, et al.⁴ The nine possible clinical states for patient agents include five in which the patient is not contagious: susceptible to colonization, non-susceptible to colonization, exposed to *C. difficile*, cleared (includes recent clearing of prior infection or colonization), and death, as well as four in which they are contagious: colonized (asymptomatic), infected (symptomatic), recolonized (sustained colonization, but asymptomatic), and recurrent infection (return of symptoms). Contagious patients can transmit *C. difficile* to nurses, doctors, visitors, and any environment they come into contact with, as well as other patients they meet in the ward common room. Conversely, they can become exposed from contaminated nurses, doctors, other patients, and the environment. Only one patient is assigned to each single-bed room at a time. Patients may change rooms within or between wards while at the hospital. These intra- and inter-ward transfers occur based on the patient transfer probabilities listed in Table 1.

Visitors: All visitors are assigned to a single patient and stay with them for an average visit duration of 15 minutes.⁵⁻⁸ Visits occur in their patient’s room or the ward common room. All visitors exit through the ward common room to leave the hospital. Visitors can become contaminated by the patient or environment they visit and can subsequently expose the environment in the patient’s room or ward common room.

Nurses: Four nurses are assigned to each ward.⁵⁻¹¹ They are based at their ward nursing workstation and leave it to care for patients in the patient rooms. Nurses only visit patients on their home ward. They spend an average of 4.7 minutes at each patient encounter.⁵⁻¹₄ Patients are visited by nurses an average of five times every six hours.⁵⁻¹₂,¹⁵,¹⁶ Like visitors, nurses can become contaminated by the patient or environment they visit. Once contaminated, they can subsequently expose other patients or the environment in patient rooms or the nursing workstation.

Doctors: Two doctors are assigned to each ward.⁵⁻¹⁷ They are based at their home ward physician workroom, but leave it to care for patients throughout the hospital. They spend an average of 10.8 minutes at each patient encounter.⁵⁻¹₄ Each patient is visited by a doctor an average of one time every six hours.⁵⁻¹₂,¹⁵,¹₆ Like visitors and nurses, doctors can become contaminated by the patient or environment they visit. Once contaminated, they can subsequently expose other patients or the environment in patient rooms or the physician workroom.

*C. difficile* transmission: Transmission occurs due to transient exposure to *C. difficile* spores from contagious patients and contaminated visitors, nurses, doctors, and the environment. The probability of contamination is proportional to the duration of exposure. Infection control interventions decrease *C. difficile* transmission by preventing (example: contact precautions) or clearing (example: hand hygiene, environmental cleaning) exposure and contamination.
**Infection control interventions:** Nine single interventions and eight multi-intervention bundles were modeled (selected parameters included in Table 1). Each single intervention was modeled at baseline, enhanced, and ideal implementation levels.

1. **Healthcare worker hand hygiene** improved nurse and physician hand hygiene compliance and increased the utilization of soap and water (versus alcohol-based hand rub) for known *C. difficile* patients.
2. **Patient hand hygiene** had similar effects on compliance and soap and water usage as the healthcare worker hand hygiene intervention, but for patient practices.
3. **Visitor hand hygiene** had similar effects on compliance and soap and water usage as the healthcare worker and patient hand hygiene interventions, but for visitor practices.
4. **Healthcare worker contact precautions** extended contact precautions for *C. difficile* patients until patient discharge, improved nurse and physician compliance, and increased the effectiveness of precautions at preventing contamination via an educational component aimed at improving donning and doffing techniques.
5. **Visitor contact precautions** had similar effects on contact precaution duration, compliance, and effectiveness as the healthcare worker contact precaution intervention, only for visitor practices.
6. **Screening** involved evaluating all asymptomatic patients for *C. difficile* colonization within 24 hours of admission via polymerase chain reaction testing of a stool sample or rectal swab. All *C. difficile* infection control policies except treatment were then implemented for any patients identified as colonized.
7. **Daily cleaning** increased the proportion of rooms cleaned daily by environmental cleaning staff and utilized sporicidal product in all patient, staff, and common rooms hospital-wide, regardless of *C. difficile* status.
8. **Terminal cleaning** increased the proportion of rooms cleaned by environmental cleaning staff at discharge, intra-ward, or inter-ward room transfer and utilized sporicidal product in all patient rooms hospital-wide, regardless of *C. difficile* status.
9. **Reducing patient transfers** decreased the rate of intra- and inter-ward transfers and prohibited room transfers for known *C. difficile* colonized or infected patients. This decreased the terminal cleaning burden for environmental cleaning staff and thus indirectly increased terminal cleaning rates.

Multiple intervention bundle strategies were developed in a stepwise approach, sequentially adding the most clinically effective enhanced single interventions until no additional effectiveness was obtained by enlarging the bundle. Hand hygiene (healthcare worker and patient hand hygiene), environmental cleaning (daily and terminal cleaning), and patient-centered (screening, patient hand hygiene, and patient transfer) bundles were also modeled, based on expert opinion that these interventions were likely to be implemented simultaneously in bundle form.

**Fixed cost:** Enhanced patient transfer had the lowest staffing requirement, at 0.25 full-time equivalents (FTE). Enhanced daily cleaning, terminal cleaning, and screening, and ideal patient transfer required 0.5 FTE. Enhanced healthcare worker, patient, and visitor hand hygiene, enhanced healthcare worker and visitor contact precautions, and ideal daily and terminal cleaning, required 0.75 FTE. Ideal screening required 1 FTE. Ideal healthcare worker, patient, and visitor hand hygiene and ideal healthcare worker and visitor contact precautions required 1.25 FTE. These staffing requirements reflect a minimum 0.5 FTE for all ideal level interventions and an additional 0.25 FTE for interventions requiring a serial implementation campaign. This additional 0.25 FTE was not included when interventions were bundled, to account for synergy between campaigns. Otherwise, all fixed costs were added at face value, regardless of the number of interventions bundled.

**Model verification and validation:** Model verification included a structured walkthrough of the code by members of the research team and iterative dynamic testing throughout the coding process using traces and animation. The validation process included parameter sensitivity analyses, cross-validation of results with the existing *C. difficile* infection control literature, face validation of the model's logic, transmission dynamics, parameters, and results by content experts during and after model development, and calibration of the discrete-time Markov chain.
# eTable 1. Transmission Parameters Estimates

| Parameter Estimates | Mean; Triangular distribution (min, max) | Source |
|---------------------|------------------------------------------|--------|
| Probability during an encounter that patient has physical contact with | Another patient: 5% per 30 min; (1, 15) Nurse: 36% per 4.7 min (26, 46) Doctor: 69% per 10.8 min (59, 79) Visitor: 65% per 15 min (55, 75) | Patient:patient; EO Others: [5] |
| Probability during an encounter that environment has physical contact with | Patient: 100%; constant; -- Nurse: 70% per 4.7 min; (60, 80%) Doctor: 90% per 10.8 min; (80, 100%) Visitor: 93% per 15 min; (83, 100%) | [5] |
| **C. difficile** transfer efficiency | Person:person 30%; (15, 45%) Person:environment 44%; (29, 59%) | Person:person: [18] Person:environment: [19] |
| Probability that skin is contaminated on | Colonized patient: 38%; (15, 60%) Active CDI patient: 70%; (60, 80%) | [20–22] |
| Probability that patient room is contaminated for | Colonized patient: 19%; (14, 35%) Active CDI patient: 47%; (36, 60%) Non-C. difficile patient: 7%; (5, 15%) | Colonized: [22–24] Active CDI: [22-27] Non-C. difficile: [23,26,27] |

*C. difficile, Clostridioides difficile; EO, expert opinion; adapted from Barker, et al.*
### eTable 2. Discounted QALY Analysis

| Intervention Strategy | Strategy compared to | Mean incremental cost (2018 USD) | Mean incremental QALY | Cost per QALY (2018 USD) |
|-----------------------|----------------------|----------------------------------|----------------------|--------------------------|
| **Enhanced-level single interventions** |                        |                                  |                      |                          |
| Enhanced daily cleaning | Baseline             | -$358,268                        | 25.3                 | Dominant                 |
| Enhanced HCW CP       | Baseline             | $87,080                          | 0.5                  | $179,019                 |
| Enhanced HCW HH       | Baseline             | -$155,575                        | 12.2                 | Dominant                 |
| Enhanced patient HH   | Baseline             | -$8,235                          | 4.4                  | Dominant                 |
| Enhanced patient transfer | Baseline              | -$19,892                         | 2.2                  | Dominant                 |
| Enhanced screening    | Baseline             | $23,763                          | 12.8                 | $1,864                   |
| Enhanced terminal cleaning | Baseline                | -$38,039                         | 8.8                  | Dominant                 |
| Enhanced visitor CP   | Baseline             | $88,863                          | -0.1                 | Dominated                |
| Enhanced visitor HH   | Baseline             | $88,745                          | 0.01                 | $8,239,801               |
| **Ideal level single interventions** |                        |                                  |                      |                          |
| Ideal daily cleaning  | Enhanced daily cleaning | $38,707                         | 1.4                  | $26,723                  |
| Ideal HCW CP          | Enhanced HCW CP      | $53,537                          | 0.3                  | $197,789                 |
| Ideal HCW HH          | Enhanced HCW HH      | -$66,808                         | 6.8                  | Dominant                 |
| Ideal patient HH      | Enhanced patient HH  | -$33,303                         | 4.0                  | Dominant                 |
| Ideal patient transfer | Enhanced patient transfer | $7,573                        | 8.0                  | $8,997                   |
| Ideal screening       | Enhanced screening   | $56,150                          | 0.4                  | $145,445                 |
| Ideal terminal cleaning | Enhanced terminal cleaning | $18,791                        | 2.5                  | $7,663                   |
| Ideal visitor CP      | Enhanced visitor CP  | $55,896                          | 0.02                 | $2,429,054               |
| Ideal visitor HH      | Enhanced visitor HH  | $55,304                          | -0.006               | Dominated                |
| **Bundled interventions** |                        |                                  |                      |                          |
| Patient and HCW HH (hand hygiene bundle) | Baseline | -$188,164                        | 15.1                 | Dominant                 |
| Patient and HCW HH (hand hygiene bundle) | HCW HH | -$32,588                         | 2.9                  | Dominant                 |
| Daily and terminal cleaning (cleaning bundle) | Baseline | -$253,982                        | 25.7                 | Dominant                 |
| Daily and terminal cleaning (cleaning bundle) | Daily cleaning | $104,285                        | 0.4                  | $247,668                 |
| Screening, patient HH, patient transfer (patient-centered bundle) | Baseline | -$35,594                         | 19.5                 | Dominant                 |
| Daily cleaning, screening | Baseline | -$172,979                        | 29.6                 | Dominant                 |
| Daily cleaning, screening | Daily cleaning | $185,288                        | 4.3                  | $43,021                  |
| Daily cleaning, screening, HCW HH | Daily cleaning, screening bundle | $79,998                        | 1.1                  | $72,919                  |
| Daily cleaning, screening, HCW HH, patient HH | Daily cleaning, screening, HCW HH bundle | $56,836                        | 0.3                  | $213,110                 |
| Daily cleaning, screening, HCW HH, terminal cleaning | Daily cleaning, screening, HCW HH, patient HH bundle | $134,921                        | 0.1                  | $1,103,008               |
| Daily cleaning, screening, HCW HH, patient HH, terminal cleaning | Daily cleaning, screening, HCW HH, patient terminal cleaning bundle | $17,761                        | 0.1                  | $321,654                 |

The trends regarding intervention cost effectiveness remain the same, while the cost per QALY increases for any given intervention under the discounted QALY analysis. CP, Contact precautions; HCW, Healthcare worker; HH, Hand hygiene; QALY, Quality-adjusted life year; USD, United States dollar

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### eTable 3. Probabilistic Sensitivity Analysis Results of Incremental Cost-effectiveness Ratios for 100,000 Runs

| Intervention Strategy                          | Strategy compared to | Mean incremental cost (2018 USD) | Mean incremental HO-CDI averted | Mean incremental QALY | Cost per HO-CDI averted (2018 USD) | Cost per QALY (2018 USD) |
|-----------------------------------------------|----------------------|----------------------------------|--------------------------------|-----------------------|-----------------------------------|------------------------|
| Enhanced daily cleaning                       | Baseline             | -$356,261                        | 25.8                           | 37.2                  | Dominant                          | Dominant               |
| Enhanced HCW CP                               | Baseline             | $87,063                          | 0.5                            | 0.7                   | $183,344                          | $125,813               |
| Enhanced HCW HH                               | Baseline             | -$156,376                        | 12.4                           | 18.0                  | Dominant                          | Dominant               |
| Enhanced patient HH                           | Baseline             | -$8,055                          | 4.2                            | 6.4                   | Dominant                          | Dominant               |
| Enhanced patient transfer                     | Baseline             | -$20,449                         | 1.7                            | 3.2                   | Dominant                          | Dominant               |
| Enhanced screening                            | Baseline             | $65,661                          | 13.5                           | 18.8                  | $4,674                            | $3,499                 |
| Enhanced terminal cleaning                    | Baseline             | -$38,335                         | 7.0                            | 13.0                  | Dominant                          | Dominant               |
| Enhanced visitor CP                           | Baseline             | $88,458                          | 0.008                          | -0.02                 | $11,563,202                       | Dominated              |
| Enhanced visitor HH                           | Baseline             | $88,212                          | 0.01                           | -0.07                 | $6,041,920                        | Dominated              |
| Enhanced-level single interventions           |                      |                                  |                                |                       |                                   |                        |
| Ideal daily cleaning                          | Enhanced daily cleaning | $38,805                         | 1.6                            | 2.3                   | $24,879                           | $17,100                |
| Ideal HCW CP                                  | Enhanced HCW CP      | $53,504                          | 0.3                            | 0.4                   | $162,870                          | $126,965               |
| Ideal HCW HH                                  | Enhanced HCW HH      | -$64,536                         | 7.0                            | 9.9                   | Dominant                          | Dominant               |
| Ideal patient HH                              | Enhanced patient HH  | -$34,115                         | 4.0                            | 6.0                   | Dominant                          | Dominant               |
| Ideal patient transfer                        | Enhanced patient transfer | $7,957                         | 0.7                            | 1.3                   | $11,219                           | $6,009                 |
| Ideal screening                               | Enhanced screening   | $56,769                          | 0.4                            | 0.4                   | $157,930                          | $127,822               |
| Ideal terminal cleaning                       | Enhanced terminal cleaning | $18,116                        | 2.0                            | 3.4                   | $9,258                            | $5,256                 |
| Ideal visitor CP                              | Enhanced visitor CP  | $55,877                          | 0.005                          | -0.03                 | $103,476,304                      | Dominated              |
| Ideal visitor HH                              | Enhanced visitor HH  | $55,919                          | -0.001                         | -0.009                | Dominated                         | Dominated              |
| Ideal level single interventions              |                      |                                  |                                |                       |                                   |                        |
| Patient and HCW HH (HH bundle)                | Baseline             | -$187,371                        | 15.3                           | 22.3                  | Dominant                          | Dominant               |
| Patient and HCW HH (HH bundle)                | HCW HH               | -$30,996                         | 2.9                            | 4.3                   | Dominant                          | Dominant               |
| Daily and terminal cleaning (environmental cleaning bundle) | Baseline             | -$252,055                        | 26.0                           | 37.8                  | Dominant                          | Dominant               |
| Daily and terminal cleaning environmental cleaning bundle | Daily cleaning | $104,207                          | 0.2                            | 0.6                   | $555,118                          | $188,412               |
| Screening, patient HH, patient transfer (patient-centered bundle) | Baseline             | $6,979                           | 19.9                           | 28.5                  | $351                              | $245                   |
| Daily cleaning, screening                     | Baseline             | -$129,150                        | 30.8                           | 43.6                  | Dominant                          | Dominant               |
| Daily cleaning, screening                     | Daily cleaning       | $227,112                         | 5.0                            | 6.4                   | $45,586                           | $35,430                |
| Daily cleaning, screening, HCW HH             | Daily cleaning, screening | $80,959                         | 1.1                            | 1.5                   | $75,204                           | $53,141                |
| Daily cleaning, screening, HCW HH, patient HH | Daily cleaning, screening, HCW HH bundle | $56,803                         | 0.3                            | 0.5                   | $180,579                          | $111,279               |
| Daily cleaning, screening, HCW HH, terminal cleaning | Daily cleaning, screening, HCW HH, patient HH bundle | $134,946                         | 0.03                           | 0.1                   | $4,069,547                        | $2,253,251             |
| Daily cleaning, screening, HCW HH, patient HH, terminal cleaning | Daily cleaning, screening, HCW HH, patient HH, terminal cleaning bundle | $17,388                         | 0.0002                          | 0.05                  | $115,921,899                      | $349,898               |
| Bundled interventions                         |                      |                                  |                                |                       |                                   |                        |
| Patient and HCW HH (HH bundle)                | Baseline             | -$187,371                        | 15.3                           | 22.3                  | Dominant                          | Dominant               |
| Patient and HCW HH (HH bundle)                | Baseline             | -$30,996                         | 2.9                            | 4.3                   | Dominant                          | Dominant               |
| Daily and terminal cleaning (environmental cleaning bundle) | Baseline             | -$252,055                        | 26.0                           | 37.8                  | Dominant                          | Dominant               |
| Daily and terminal cleaning environmental cleaning bundle | Daily cleaning | $104,207                          | 0.2                            | 0.6                   | $555,118                          | $188,412               |
| Screening, patient HH, patient transfer (patient-centered bundle) | Baseline             | $6,979                           | 19.9                           | 28.5                  | $351                              | $245                   |
| Daily cleaning, screening                     | Baseline             | -$129,150                        | 30.8                           | 43.6                  | Dominant                          | Dominant               |
| Daily cleaning, screening                     | Daily cleaning       | $227,112                         | 5.0                            | 6.4                   | $45,586                           | $35,430                |
| Daily cleaning, screening, HCW HH             | Daily cleaning, screening | $80,959                         | 1.1                            | 1.5                   | $75,204                           | $53,141                |
| Daily cleaning, screening, HCW HH, patient HH | Daily cleaning, screening, HCW HH bundle | $56,803                         | 0.3                            | 0.5                   | $180,579                          | $111,279               |
| Daily cleaning, screening, HCW HH, terminal cleaning | Daily cleaning, screening, HCW HH, patient HH bundle | $134,946                         | 0.03                           | 0.1                   | $4,069,547                        | $2,253,251             |
| Daily cleaning, screening, HCW HH, patient HH, terminal cleaning | Daily cleaning, screening, HCW HH, patient HH, terminal cleaning bundle | $17,388                         | 0.0002                          | 0.05                  | $115,921,899                      | $349,898               |

CP, Contact precautions; HCW, Healthcare worker; HH, Hand hygiene; QALY, Quality-adjusted life year; USD, United States dollar
eFigure 1. Schematic of the 200-Bed Model Hospital and Possible Agent Movement

N: Nurse; 4 per ward
D: Doctor; 2 per ward
P: Patient
V: Visitor
Nurses only visit patients on their home ward

Visitors all exit through common room
Patients can change rooms within wards and visit the common room
Doctors have visit patients hospital a home ward, but throughout the

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One-way sensitivity analyses were based on 5,000 runs of each enhanced level cost-saving intervention, compared to baseline. The interventions were most sensitive to hospitalization costs. CDI, *Clostridioides difficile* infection; HCW: Healthcare worker; PCR, polymerase chain reaction; QALY, Quality-adjusted life year.
One-way sensitivity analyses were based on 5,000 runs of both enhanced level interventions, compared to baseline. Screening at admission was most sensitive to increased PCR testing costs. The visitor hand hygiene and healthcare worker contact precautions interventions resulted in minimal improvement in QALYs saved, thus were most sensitive to changes in age-related utility values. Visitor contact precautions is not shown, because the intervention is dominated. CDI, *Clostridioides difficile* infection; PCR, polymerase chain reaction; QALY, Quality-adjusted life year.
eFigure 4. Incremental Cost-effectiveness of 100 000 Runs of the Probabilistic Sensitivity Analysis

HCW, Healthcare worker; QALY, Quality-adjusted life year

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