Using an agent-based simulation model to conduct an economic analysis of strategies to control *Clostridium difficile* transmission and infection

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Background

- ***C. difficile* infection (CDI)** is one of the most common and important types of healthcare-associated infection (HAI) among patients hospitalized in the US [1].
- *C. difficile* is acquired exogenously, although its reservoir of infection is the hospital and other care facilities. The risk of acquiring the organism increases linearly with the length of hospital stay [2].
- The association of CDI with prolonged hospital stays and increased healthcare costs [3,4] underscores the urgent need for improved hospital infection control practice.
- The infection control community is highly divided on the most appropriate strategy to control transmission of *C. difficile* within healthcare institutions.
- Few studies have been conducted to assess the cost-effectiveness of prevention strategies to control transmission of *C. difficile*.

Objective

To assess the cost-effectiveness of bundling strategies for reducing *C. difficile* transmission and infection. The strategies comprising the bundle included:

1. **Aggressive and early testing for *C. difficile***
2. **Empiric isolation and treatment of symptomatic patients**
3. **Improved adherence with hand hygiene**
4. **Improved use of soap and water for hand hygiene for contacts with CDI patients**
5. **Improved adherence with contact precautions for contacts with CDI patients**
6. **Improved environmental decontamination**

Agent–Based Simulation

- Agent-based simulation (or agent-based modeling (ABM)) is a class of computer modeling that is useful for studying complex, dynamic systems.
- ABMs support a realistic representation of systems such as healthcare delivery environments and provide inexpensive laboratories where decision makers can conduct "what-if" experimentation.
- ABMs differ from traditional mathematical models such as equation-based or compartmental models.
- ABMs begin with a collection of autonomous, decision-making agents which exist and interact with an environment.
- Each agent is assigned a set of behaviors and parameters which govern their interactions with other agents.
- With ABMs, system-level observables emerge from these individual actions and interactions with the relationships among the obserables at ethe model output.
- ABMs are thus "simulations based on the global consequences of local interactions of members of a population."
- ABM are often constructed in **Anylogic 6.5** (XJ Technologies, St. Petersburg, Russia) using Java-based graphical editing tools to create replicated agents and their associated parameters, variables, and statecharts.

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Methods

Simulation model

- Agent classes included patients, nurses, physicians, and rooms (**Figure 1**).
- Each agent existed in explicit "states" governed by statecharts; transitions between states were treated as discrete events that occur probabilistically.
- The various components of the model were divided into a series of static and dynamic "sub-models".
- **Healthcare workers** served as vectors of contagion. **Figure 1A** shows the contact network between healthcare workers and patients.
- **Hospital room** occupancy was governed by a submodel directing patient flow regarding admission, room transfer, and discharge (**Figure 1B**). Rooms were also given the capacity to hold dynamic quantities of *C. difficile* (**Figure 1C**).
- **Patients** moved within and across wards in the hospital. Patients could acquire *C. difficile* asymptomatically through contact with healthcare workers or the room environment (**Figure 1D**), and could then progress to symptomatic CDI with shedding of organisms into the room environment.
- **Antibiotics** were given to patients during their stay and impacted the acquisition, progression to symptomatic CDI, and organism shedding (**Figure 1C**). Treatment also led to decreased shedding into the environment (**Figure 1E**).
- ***C. difficile*** has strain properties, can be imported into the hospital, can be transmitted, can be an etiology of asymptomatic and symptomatic infection, and can be detected by diagnostic testing.

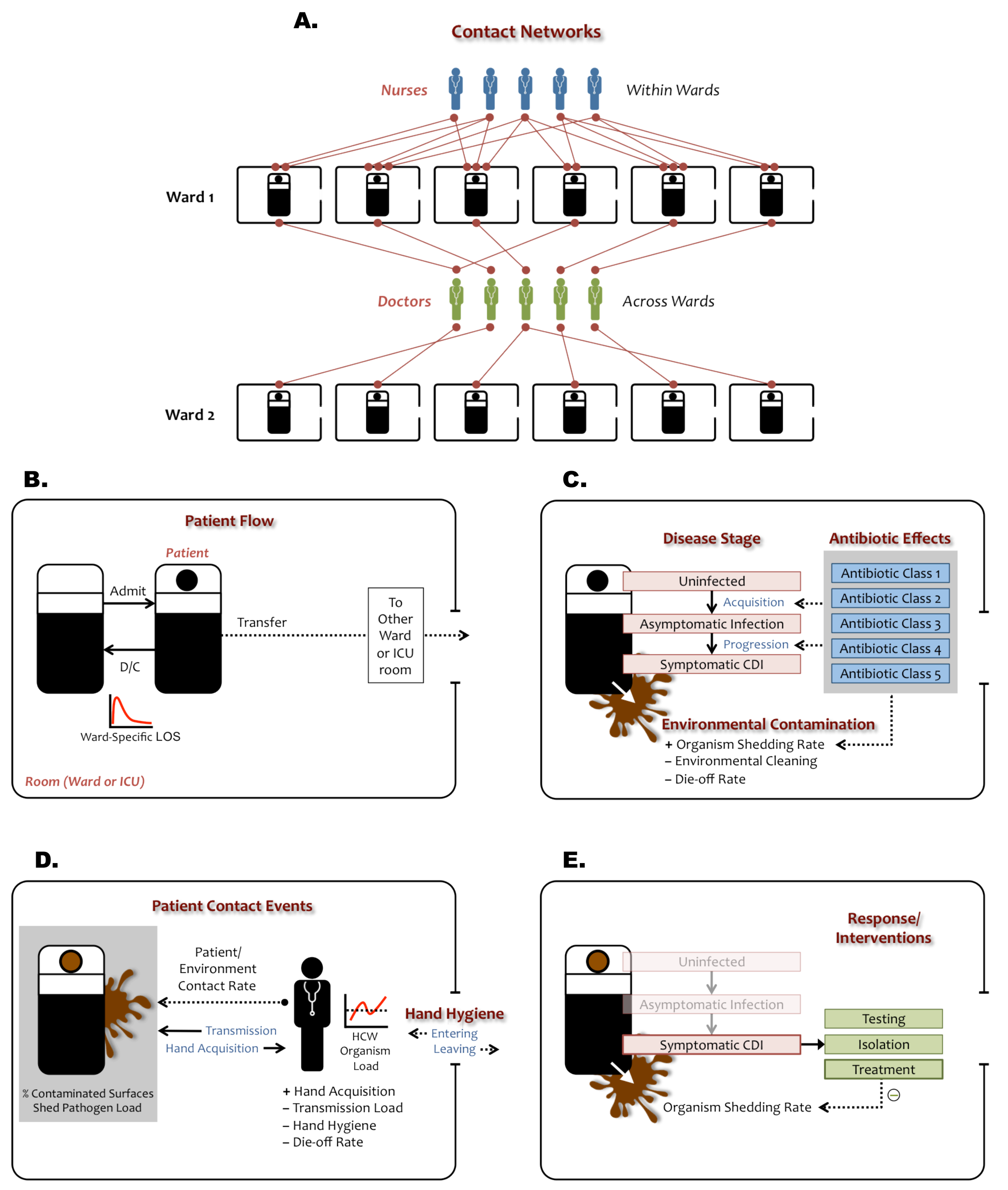

Figure 1: Key agents and submodels.

Methods

Intervention strategies

- The economic analysis compared the costs and the outcomes associated with 3 levels of the bundled infection control strategies:
- **Base-case (BASE)** strategy reflects current realities in a typical hospital not employing interventions specifically targeting *C. difficile*.
- **Intermediate (INT)** represent an improvement over BASE parameter values, reflecting the reasonably expected effect from typical adherence to hospital-side effort focusing on that particular strategy.
- **Optimal (OPT)** represent maximum effects that can be reasonably expected from strong adherence to an intensive and aggressive campaign to reduce *C. difficile* transmission.

Economic analysis

- In addition, we varied 2 key model parameters to capture the differences in our results based on different epidemiologic conditions: **transmission** and **importation**.
- We assumed 3 levels for both of these key parameters: **low**, **medium**, **high**.
- We ran a total of 100 iterations of the model for each intervention strategy, each transmission parameter value, and each importation parameter value. In other words, we ran a total of 2700 iterations of the model.
- For each of the 27 unique combinations of strategies and epidemiologic conditions, averages of the 100 iterations were used as inputs to the economic analysis.
- Costs were taken from the hospital perspective and were converted to 2011 US dollars.
- Results from the economic analysis were presented as incremental cost-effectiveness ratios (ICERs), defined as the difference in the incremental cost of two interventions divided by the incremental difference in the effectiveness of two interventions.

Table 1: Key parameter inputs

Parameter	Strategy			Source
	BASE	INT	OPT	
Hand hygiene				
Nurses, before patient contact	30/50	60/70	80/90	[5-8]
Nurses, after patient contact	50/70	70/80	90/90	[5-8]
Physicians, before patient contact	20/30	50/60	70/70	[5-8]
Physicians, after patient contact	40/50	70/80	80/80	[5-8]
Soap and water	60	80	90	Model
Contact precautions	60	75	90	[9]
Environmental cleaning				
Routine daily (e.g., detergent-based)	27.5	30	35	[10-14]
Routine terminal (e.g., detergent-based)	35	40	42.5	[10-14]
Deep terminal (e.g., chlorine-based)	70	80	90	[10-14]
Testing	1.5	1	0.5	[15-17]
Empiric isolation and treatment	No	Yes	Yes	Model

Note: For hand hygiene intervention, values = % adherence in non-isolation/isolation rooms. For soap and water intervention, values =% use of each. For contact precautions intervention, values =% adherence. For environmental cleaning intervention, values =% organism reduction. For testing intervention, values =mean time (days) from symptom to test order.

- **Table 1** provides some of the key parameter values used for the BASE, INT, and OPT scenarios in the simulation.
- Parameters were estimated from values in the literature or from input from an expert panel.

Methods

Economic analysis, continued

- Cost input parameters are shown in **Table 2**.
- The inputs are categorized based on the strategy to which the pertain.
- The highest cost was that of a *C. difficile* Infection ($17,037).

Table 2: Cost inputs

Parameter	Cost	Source
Hand hygiene		
Variable cost per application	$0.07	[18]
Fixed costs for hand hygiene promotion campaign	$54,284	[19]
Soap and water		
Variable cost per application	$0.07	[18]
Contact precautions		
Gloves (per pair)	$0.09	[20]
Gown	$0.92	[20]
Environmental cleaning		
Routine daily cleaning	$22.33	[21]
Routine terminal cleaning	$36.52	[21]
Deep terminal cleaning	$172.95	[21]
Testing		
PCR test	$7.66	[22]
Technician wage	$17.96	BLS
Technician time (minutes)	11	[22]
Treatment of symptomatic patients		
Vancomycin (oral)	$1,347	[23]
***C. difficile* infection**	$17,037	[24]

Results

Effectiveness parameter = infections averted

- The results of the cost-effectiveness analysis for the infections averted effectiveness measure are shown in **Table 3**.
- This table presents ICERs for (1) INT compared to BASE, (2) OPT compared to BASE, and (3) OPT compared to INT.
- These ICERs are shown for combinations of the three levels of the transmission and importation parameters.

Table 3: Results. Effectiveness measure = infections averted

Importation	Transmission		
	Low	Medium	High
INT vs. BASE			
Low	$7,269	$3,580	Dominant
Medium	Dominant	Dominant	Dominant
High	Dominant	Dominant	Dominant
OPT vs. BASE			
Low	$36,662	$28,789	Dominant
Medium	Dominant	Dominant	Dominant
High	Dominant	Dominant	Dominant
OPT vs. INT			
Low	$321,598	$305,295	$80,902
Medium	$59,077	$52,329	$12,577
High	$24,952	$21,049	$2,357

- For high levels of transmission and medium and high levels of importation, both INT and OPT were dominant (i.e., more effective and less costly) compared to BASE.
- Compared to INT, OPT was both more effective and more expensive. The ICERs for OPT ranged from $2,357-$321,598/infection averted.

Results

Effectiveness parameter = QALY

- The results of the cost-effectiveness analysis for the infections averted effectiveness measure are shown in **Table 4**.

Table 4: Results. Effectiveness measure = QALY

Importation	Transmission		
	Low	Medium	High
INT vs. BASE			
Low	$724,941	$357,031	Dominant
Medium	Dominant	Dominant	Dominant
High	Dominant	Dominant	Dominant
OPT vs. BASE			
Low	$3,656,208	$2,871,040	Dominant
Medium	Dominant	Dominant	Dominant
High	Dominant	Dominant	Dominant
OPT vs. INT			
Low	$32,071,936	$30,446,070	$8,068,107
Medium	$5,891,529	$5,218,615	$1,254,265
High	$2,488,412	$2,099,186	$235,033

- For high levels of transmission and medium and high levels of importation, both INT and OPT were dominant compared to BASE.
- Compared to INT, the ICERs for OPT ranged from $235,033-$32,071,936/ QALY.

Summary & Conclusions

- Using a dynamic cost-effectiveness analysis, we find that bundled interventions to prevent CDI are likely to reduce costs and CDI under normal to high importation prevalence and transmissibility.
- These results hold for quality-of-life outcomes as well.
- Optimal levels of adherence to interventions come at an increased cost that does not necessarily translate to increased effectiveness compared to intermediate levels. This suggests that Intermediate levels of adherence to the interventions described here may be sufficient to achieve desirable outcomes.

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