**Appendix. Overview, Design Concepts, Details (ODD) Protocol**

The ODD protocol provides a standardized way of describing an agent-based model (ABM) so that other researchers can implement the model, promoting open science and replicability [1, 2]. Model source code and supporting data can be found at the following location: <https://github.com/RTIInternational/NCMInD>

***i. Purpose and scope.*** We use a geospatially explicit ABM to *Clostridioides* *difficile* (*C. difficile*) infection (CDI) with a disease model derived from a previously published CDI compartmental model [4]. This natural history model is based on four key assertions regarding *C. difficile*. First, risk factors for CDI include the use of antibiotics, advanced age, exposure to inpatient healthcare settings, and underlying concurrent medical conditions [5, 6]. Second, individuals who are exposed to antibiotics have residual increased risk of CDI for up to 90 days following the end of treatment therapy [7, 8]. Third, *C. difficile* asymptomatic colonization, when a person tests positive for the *C. difficile* organism or its toxin but exhibits no clinical symptoms, is a necessary step to develop CDI [9]. Fourth, *C. difficile*-infected individuals are typically treated with one or more antibiotics during their infection and recovery [10].

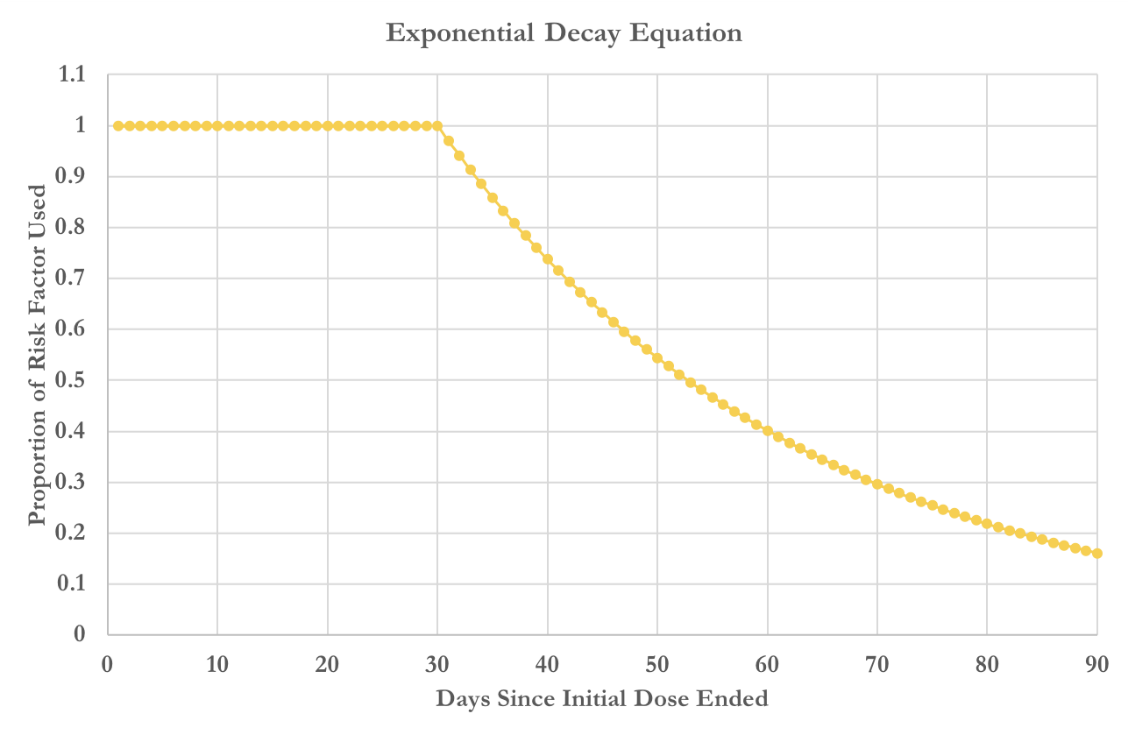
***ii. Entities, state variables, and scales.***The ABM has two types of entities: locations and agents. Locations are represented by the 14 static nodes of the geospatially explicit healthcare network of UNC Health Care in North Carolina (NC) [11]. Because between- and within-household infection dynamics are not currently modeled, all households are assigned to a single community node. Agents are initialized using the NC synthetic population and defined by sex (female, male); age group in years (<50, 50−64, ≥65 years); race (white, black, other race); and NC home county of residence (100 NC counties), creating 1,800 unique demographic combinations. Agents can move among different locations and can change both disease and antibiotic-use states. The ABM is implemented with a 1-day time step and a 1-year time horizon. That is, agents may change states once every day. The variables that drive an agent’s movement among locations (sex, age group, race, and NC county of residence) are not updated during the 1-year model run. Comorbidities are assigned to select agents based on published proportions [4]. An agent’s probability of moving is also informed by its comorbidity status. For example, the presence of comorbidities increases the probability of an agent changing location to a short-term acute care hospital (STACH).

***iii. Submodels:*** The ABM has two submodels, a location model and a CDI disease model.

The ***location model*** defines agent movement on the location network. Each agent may move to any other available location from its initialized location (**Appendix Figure 1**). There are 14 possible locations: 1 node representing the community, 10 nodes representing each of the UNC Health Care-affiliated STACHs (UNC STACHs), 1 node representing all other NC STACHs (non-UNC STACH), 1 node representing all NC long-term acute care hospitals (LTACH), and 1 node representing all licensed NC nursing homes. When an agent arrives at a healthcare facility, the agent is assigned a LOS based on gamma distributions unique to the healthcare facility. Patient-level data, available for 7 of the 10 UNC STACHs, were used to obtain hospital-specific LOS gamma distributions fitted to these patient-level data. For the remaining three UNC STACHs and the non-UNC STACHs, aggregate discharge data was used to estimate the parameters of a gamma distribution because patient-level data were not available [12]. In the current model, the LOS is not dependent on disease state, unless an agent develops CDI. Upon developing CDI an agent’s LOS is increased by 3 days [13, 14]. When an agent’s LOS is complete, the agent moves from the healthcare facility. The agent cannot remain at the healthcare facility past their assigned LOS. However, agents can move among non-UNC STACHs and remain at the non-UNC STACH node. When the agent moves to another healthcare facility, they are assigned a new LOS. We simulate agent movement based on the following agent characteristics: (1) current location, (2) NC home county of residence, (3) sex (male, female), (4) age group in years (<50, 50-64, ≥65 years), (5) race (white, black, other race), and (6) presence of comorbidities (yes, no) (**Appendix Table 1**).

A ***CDI disease model***, derived from Durham and colleagues’ CDI compartmental model, is implemented in the ABM [4]. In our disease model, agents can move between one of the following four disease states: (1) susceptible, (2) asymptomatically colonized, (3) CDI, and (4) death associated with CDI (**Appendix Figure 2, Appendix Table 2**). Each agent exists in a dynamic, binary state of antibiotic exposure (i.e., with antibiotic exposure or without antibiotic exposure). Daily probabilities of antibiotic exposure are informed by agent location and age. When assigned to antibiotic exposure, an agent is further assigned to one of three antibiotic risk levels, low, moderate, and high risk (**Appendix Tables 2 and 3**) of antibiotics while in any one of the first three CDI states. Agents that reach the CDI state are subsequently assigned a new course of antibiotics. The probability of receiving antibiotics depends on the current location of the agent, with agents in the community (i.e., those receiving outpatient antibiotics) having probabilities additionally informed by age. Antibiotic exposure duration is approximately 100 days. Agents receive an initial course of antibiotics from a normal distribution (mean 10 days, standard deviation of 2 days) and are at increased risk for 90 days after their initial course ends. Antibiotic risk exponentially decays from day 30 through day 90 with each day’s value equal to 97% of the previous day. By ensuring that each day’s probability is 97% of the previous day’s value, we obtain a curve that produces the same CDI counts as that of the original 60-day method. The proportion of the antibiotic risk factor that is used for *x* days after an agent’s initial dose ends is shown in **Equation 1 (with figure).**

**Equation 1.**



Once an agent’s current course of antibiotics ends, an agent may be assigned to a subsequent course. If assignment occurs during the residual risk period, the highest risk level of the two possible antibiotic risk levels is assigned to the agent.

Agents can recover from CDI and later return to the CDI state any number of times (i.e., recurrent CDI). Previous CDI occurrences and age ≥65 years increase an agent’s probability of recurrent CDI. Force of colonization is the probability that an uncolonized agent becomes asymptomatically colonized with *C. difficile* and is based on an agent’s location (STACH, LTACH, nursing home, community), including the number of patients at that location that are colonized and that have CDI. **Equation 2** shows an example of this calculation based on the STACH location [4].

**Equation 2.**

In this way, the ABM framework of agent flow through the network is linked to the CDI disease model. The probability that an asymptomatically colonized patient develops CDI is determined by the agent’s antibiotic exposure status, age, presence of comorbidities, recent CDI, and location [4].

We apply our CDI disease model based on the following agent attributes: (1) location state; (2) antibiotic state (i.e., currently exposed or currently not exposed); (3) number of recurrent CDI events, defined as CDI event(s) within 14 days to 56 days of a previous CDI event (up to three; each additional recurrent CDI event will initiate a new 14−56 day window); and (4) comorbidities (i.e., presence or absence) [4, 15, 16]. We assign the presence of comorbidities to agents at model initialization, such that 23.74% of agents 50-64 years of age and 54.97% of agents ≥65 years of age have comorbidities [4]. We then apply a multiplier to all agents’ location transition probabilities, such that at any given time in the model, 55% of agents in healthcare facilities who are 50-64 years of age and 79% of agents in healthcare facilities who are ≥65 years of age will have comorbidities [4].

***iv. Initialization.*** The ABM is initialized with a geospatially explicit synthetic baseline population of NC based on the United States synthetic population [17]. To initialize other agent variables (e.g., initial location, disease state)), we merged initialization variables to the synthetic population using various data sources. First, agent locations are initialized using steady-state values for locations based on available data [12, 18, 19, 20]. Agents located in healthcare facility nodes are assigned a LOS based on the LOS distribution for that location. All agents are initialized without exposure to antibiotics and are either susceptible or asymptomatically colonized. Colonization prevalence is assigned randomly to each agent based on its location. The rate of colonization assignment is based on published data [4].

***v. Process overview and scheduling.*** A simulation run first updates the location of an agent, then the agent’s life status and finally the agent’s disease state.Agent locations are updated based on state transition matrices parameterized with the following data sources: (1) aggregate hospital discharge data for NC [12, 18]; (2) published demographic characteristics of nursing home residents and LTACH patients [19, 20]; (3) NC licensed healthcare facility characteristics (i.e., capacity and occupancy) [19, 21, 22]; and (4) de-identified patient-level hospital discharge data from UNC Health Care (July 1, 2016−June 30, 2017). Using the NC synthetic population, marginal population distributions were calculated by sex, age group, race, and NC home county of residence. Iterative proportional fitting was used to estimate the joint multidimensional distribution of agents by county, sex, age group, and race, and to estimate the flow of these agents among the 14 location nodes (transition probabilities) [23]. In the case of small cell counts in the multidimensional tables, we used maximum likelihood estimation of an additive multinomial model to estimate the county-level transition probabilities to and from STACHs [24]. All cells had a minimal value of three agents [25].

Because an infectious disease state may lead to death, the life status of an agent is updated prior to an update to its disease state, simulating death from non-CDI related causes. Probabilities for transition to adjacent states depend on the current disease state of an agent (**Appendix Figure 2**). For recurrent CDI events, an agent first must leave the CDI state. Upon becoming colonized again, either directly from the CDI state or through the susceptible state, an agent can move back to the CDI state with an increased probability of CDI. If exposed to antibiotics, we use **Equation 1** to calculate the probability of moving from colonized to CDI.

***vi. Input data.*** The model does not use input data to represent time-varying processes.

***vii. Agent interactions and organism transmission.*** Agents do not make explicit decisions. Agents do interact with their environment and, through their environment, interact with each other. **Equation 2** is based on the disease status of all the agents currently at a healthcare facility location node. Therefore, an agent’s probability of becoming colonized is influenced by the current status of the other agents at that same location.

***viii. Stochasticity.*** Stochasticity in the ABM results from random probabilities used to determine the following: (1) location changes, (2) disease state changes (including antibiotic exposure), (3) death, (4) agent initialization, and (5) LOS.

***viv. Model verification, validation, and calibration.*** Prior to calibrating the location and disease submodels we verified that simulation runs produced reasonable output of expected values. This was achieved by testing individual methods implemented in those submodels and running the entire model. Once verified, we calibrated the model according to specific targets derived from the literature and expert opinion. We used a compartmental flow calculation to calibrate agent flow among the healthcare facilities and the communities. This compartmental calculation consisted of applying the current probability of movement from the community to all agents and assessing the final total proportion of patients that moved to each location node. We subsequently applied the current probabilities of patients leaving each facility to determine the proportion of agents leaving each facility node. These calculations resulted in overall probabilities that we compared to our target probabilities. Throughout this process, we made minor adjustments to multipliers that effect transition probabilities until the movement in the compartmental flow model matched our calibration targets (**Appendix Table 4**).

For the disease model, we verified that antibiotics exposure was occurring at reasonable rates by comparing the total number of antibiotic prescriptions at each location to published data. Subsequently, we calibrated colonization prevalence rates based on location (4). Because the colonization rate is determined by the force of colonization equation, we created facility-specific multipliers to finely adjust colonization rate, rather than adjusting colonization clearance rates. Colonization is not a rare occurrence in the ABM, ranging from 6% to 15% according to location. This facilitated us conducting numerous, small model runs to adjust each multiplier until all locations matched their colonization prevalence values.

For CDI we derived two sets of targets based on different CDI surveillance case definitions (**Appendix Table 5**). We used healthcare-associated CDI (HA-CDI) and community-associated CDI (CA-CDI) to calculate incidence per 100,000 persons [15, 26-28]. We used healthcare (hospital)-onset (HO-CDI) and community-onset (CO-CDI) to calculate incidence per 10,000 patient-days [29, 30]. To match CA-CDI and CO-CDI cases targets, the model randomly assigns CDI to a small number of agents.

To calibrate to these targets, we again created multipliers to adjust the transition to CDI, based on location. CDI incidence is a rare occurrence in the ABM, with only 5 cases per 10,000 patient-days to 10 cases per 10,000 patient days. Therefore, conducting numerous, small runs to for calibration was not feasible. Instead, we completed several, larger runs using a random sample of 2,000,000 agents from the NC synthetic population. As CDI incidence fluctuates greatly across model run, we updated multipliers until all targets were within 15% of a single model run.

**Appendix Table 1: Location model variables**

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | Description | Possible Values | Source |
| id | Identifier for each agent | [0, …) | model generated |
| age group | categorical age (years); fixed | [0(<50), 1(50-64), 2(65+)] | synthetic population |
| demographic id | a single value representing an agent’s age, sex, race, and North Carolina home county | [0, 1, 800] | synthetic population |
| community probability | daily probability that an agent leaves the community and moves to a healthcare facility | (0, 1) | *(15-18),* de-identified patient-level hospital discharge data from UNC Health Care (July 1, 2016−June 30, 2017) |
| location status | current location of the agent | [0, …) | *model generated* |
| life status | current life status of the agent | [0 (dead), 1 (alive)] | *model generated* |
| current los | current length of stay for an agent; value of -1 if the agent is not at a healthcare facility | [-1, 1, …] | *(15-18),* de-identified patient-level hospital discharge data from UNC Health Care (July 1, 2016−June 30, 2017) |
| nh patient | binary flag signifying if the agent is current in a nursing home | [0 (no), 1 (yes)] | model generated |
| leave facility day | day in the model that an agent will leave a healthcare facility; set when an agent changes location | [0, …) | model generated |
| death probability | daily probability that an agent dies; based on location and demographics | (0, 1) | *(26)* |

**Appendix Table 2: *Clostridioides difficile* infection (CDI) disease model and antibiotic parameters**

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter | Description | Possible Values | Source |
| CDI Base Rate (Community) | Transition from colonized to CDI | 0.0000063 | 4 |
| CDI Base Rate (Hospital) | Transition from colonized to CDI | 0.00021 |
| CDI Base Rate (NH) | Transition from colonized to CDI | 0.0000860 |
| CDI Recovery | Transition from CDI to another state | 0.09426 |
| Recurrence | Transition from colonized to CDI for patients with a recent CDI | 0.1219 |
| Colonization Initialization (Community) | Colonization prevalence | 0.066 |
| Colonization Initialization (STACHs) | Colonization prevalence | 0.11 |
| Colonization Initialization (LTCFs) | Colonization prevalence | 0.148 |
| Colonization recurrence (1 recent CDI) | Colonization recurrence rate for agents with a recent CDI | 0.22 |
| Colonization recurrence (2 recent CDI) | Colonization recurrence rate for agents with a recent CDI | 0.33 |
| Colonization recurrence (3 recent CDI) | Colonization recurrence rate for agents with a recent CDI | 0.56 |
| Colonization clearance | Clearance to susceptible | 0.0198 |
| Base colonization rate (community) | Transition from susceptible to colonized | 0.00119928 |
| Base colonization rate (STACHs & LTACHs) | Used in the force of colonization equation | 0.022737516 |
| Base colonization rate (NHs) | Used in the force of colonization equation | 0.003693163 |
| Relative risk (concurrent conditions) | Increases risk of transitioning from colonized to CDI | 2.6 |
| Relative risk (age, 50-64) | Increases risk of transitioning from colonized to CDI | 2.2 |
| Relative risk (age, 65+) | Increases risk of transitioning from colonized to CDI | 2.9 |
| Antibiotic prescribing rates | for non-network STACHs, LTACHs, and community | Non-network STACH:  LTACH:  Nursing home:  Community, <50 years of age: 1.3x103  Community, 50-64 years of age: 1.4x103  Community, ≥65 years of age:1.7x103 | *32* |
| Antibiotic course | - | 10 days (SD = 2 days) | Expert opinion |
| Antibiotic risk ratios | - | Low risk: 2  Moderate risk: 5  High risk: 12 | *3, 39* |
| Baseline relative proportion of antibiotic risk | By location | STACHs and LTACHs: low risk = 0.4, moderate risk = 0.3, high risk = 0.3. | Patient-level data; *39* |

**Appendix Table 3. Proportion of antibiotics administered by risk level and location**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Low risk** | **Moderate risk** | **High risk** |
| **Community\*** | 0.1 | 0.6 | 0.3 |
| **LTACH** | 0.1 | 0.6 | 0.3 |
| **Nursing Home** | 0.1 | 0.6 | 0.3 |
| **STACH** | 0.4 | 0.3 | 0.3 |
| \*Represents outpatient prescribing  STACH: short-term acute care hospital  LTACH: Long-term acute care hospital | | | |

**Appendix Table 4. Calibration target percentages for agent movement**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **From Location** | **To: Community**  **(%)** | **To: UNC STACHs**  **(%)** | **To: non-UNC STACHs**  **(%)** | **To: LTACH**  **(%)** | **To: Nursing home**  **(%)** |
| **Community** | 0 | 13.41 | 85.97 | 0 | 0.62 |
| **UNC STACH** | 90.62 | 3.20 | 4.13 | 0.34 | 1.61 |
| **Non-UNC STACH** | 90.68 | 0.59 | 6.64 | 0.34 | 1.61 |
| **LTACH** | 47.47 | 0.89 | 6.22 | 0 | 45.35 |
| **Nursing home** | 25 | 9.32 | 65.68 | 0 | 0 |
| UNC STACH: UNC Health Care short-term acute care hospital (combined across all 10 UNC STACHs in the agent-based model)  Non-UNC STACH: All other North Carolina STACHs  LTACH: Long-term acute care hospital | | | | | |

**Appendix Table 5: Disease model CDI calibration targets and achieved values**

|  |  |  |
| --- | --- | --- |
| **Metric** | **Target** | **Achieved value** |
| Community-associated CDI | 30 cases to 120 cases per 100,000 agents | 78.9 cases per 100,000 agents |
| Healthcare-associated CDI | 50 cases to 160 cases per 100,000 patients | 87.8 cases per 100,000 patients |
| Community-onset CDI for UNC STACHs | 12.12 cases per 10,000 patient-days | 12.3 cases per 10,000 patient-days |
| Community-onset for non-UNC STACHs | 12.95 cases per 10,000 patient-days | 12.9 cases per 10,000 patient-days |
| Hospital-onset for UNC STACHs | 6.32 cases per 10,000 patient-days | 6.1 cases per 10,000 patient-days |
| Hospital-onset for non-UNC STACHs | 6.88 cases per 10,000 patient-days | 7.4 cases per 10,000 patient-days |
| UNC STACH: UNC Health Care short-term acute care hospital (combined across all 10 UNC STACHs in the agent-based model)  Non-UNC STACH: All other North Carolina STACHs | | |

**Appendix Figure 1. Location entities and possible agent transitions in the agent-based model.**

|  |
| --- |
| **R:\Translation and Communications\Manuscripts\Creation of HAI ABM\UPLOAD\UPLOAD_first submission\RheaFig1b.tif** |
| STACH: short-term acute care hospital; LTACH: long-term acute care hospital; NH: nursing home; 10 UNC STACHs: 10 locations representing each of the STACHs of the regional healthcare network; Non-UNC STACH: one location representing all other North Carolina STACHs |

**Appendix Figure 2. *Clostridioides difficile (C. difficile)* disease model diagram with parameters**

|  |
| --- |
| **R:\Translation and Communications\Manuscripts\Antimicrobial Stewardship\Drafts\7. Figures\Appendix CDI dis state.tif** |
| |  |  |  | | --- | --- | --- | | Parameter | Description | Source | | λ | Force of colonization by location (community, STACH, LTACH, NH) | *(4)* | | δ | Spontaneous clearance of *C. difficile* colonization | *(4)* | | μ | Relative risk for developing CDI (μA while receiving antimicrobial drugs; μ50 among persons 50–65 years of age vs. those <50 years of age; μ65 among persons >65 years of age vs. those <50 years of age) | *(4)* | | q | Probability that recovered patients show recurrence | *(4)* | | r | Probability that a patient recovering from primary CDI will have at least 1 recurrence | *(4)* | | γ | Probability of recovery from CDI | *(4)* | | α | All-cause CDI mortality | *(4)* | |
| CDI: *Clostridioides* *difficile* infection  STACH: short-term acute care hospital  LTACH: long-term acute care hospital  NH: nursing home |

**References**

1. Grimm V, Berger U, Bastiansen F, Eliassen S, et al. A standard protocol for describing individual-based and agent-based models. Ecological Modeling. 2006;198: 115-126.

2. Grimm V, Berger U, DeAngelis DL, Polhill JG, Giske J, Railsback SF. The ODD protocol: A review and first update. Ecological Modelling. 2010;221(23): 2760-2768. doi: 10.1016/j.ecolmodel.2010.08.019

4. Durham DP, Olsen MA, Dubberke ER, Galvani AP, Townsend JP. Quantifying transmission of *Clostridium difficile* within and outside healthcare settings. Emerg Infect Dis. 2016 Apr;22(4): 608-616. doi: 10.3201/eid2204.150455

5. Dubberke ER, Yan Y, Reske KA, Butler AM, Doherty J, Pham V, et al. Development and validation of a *Clostridium difficile* infection risk prediction model. Infect Control Hosp Epidemiol. 2011 Apr;32(4): 360-366. doi: 10.1086/658944

6. Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. N Engl J Med. 2005 Dec 8;353(23): 2442-2449. doi: 10.1056/NEJMoa051639

7. Hensgens MP, Goorhuis A, Dekkers OM, Kuijper EJ. Time interval of increased risk for *Clostridium difficile* infection after exposure to antibiotics. J Antimicrob Chemother. 2012 Mar;67(3): 742-748. doi: 10.1093/jac/dkr508

8. Brown KA, Fisman DN, Moineddin R, Daneman N. The magnitude and duration of *Clostridium difficile* infection risk associated with antibiotic therapy: a hospital cohort study. PLoS One. 2014;9(8): e105454. doi: 10.1371/journal.pone.0105454

9. Riggs MM, Sethi AK, Zabarsky TF, Eckstein EC, Jump RL, Donskey CJ. Asymptomatic carriers are a potential source for transmission of epidemic and nonepidemic *Clostridium difficile* strains among long-term care facility residents. Clin Infect Dis. 2007 Oct 15;45(8): 992-998. doi: 10.1086/521854

10. McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018 Mar 19;66(7): e1-e48. doi: 10.1093/cid/cix1085

11. UNC Health Care. Preparing for the future of health care. UNC health care 2017 annual report. 2017 [cited January 21 2019]. Chapel Hill, NC: UNC Health Care. Available: <https://www.unchealthcare.org/app/files/public/10436/PDF-MedCtr-Annual-Report-2017.pdf>.

12. Cecil G. Sheps Center for Health Services Research, University of North Carolina at Chapel Hill. Patient county of residence by hospital (October 1, 2014 through September 30, 2015). 2015 [cited January 28 2018]. Chapel Hill, NC: Cecil G. Sheps Center for Health Services Research, University of North Carolina at Chapel Hill. Available: <http://www.shepscenter.unc.edu/wp-content/uploads/2013/05/ptorg_pt_res_by_hosp_2015.pdf>.

13. Dubberke ER, Butler AM, Reske KA, Agniel D, Olsen MA, D'Angelo G, et al. Attributable outcomes of endemic Clostridium difficile-associated disease in nonsurgical patients. Emerg Infect Dis. 2008 Jul;14(7): 1031-1038. doi: 10.3201/eid1407.070867

14. Kyne L, Hamel MB, Polavaram R, Kelly CP. Health care costs and mortality associated with nosocomial diarrhea due to Clostridium difficile. Clin Infect Dis. 2002 Feb 1;34(3): 346-353. doi: 10.1086/338260

15. Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of *Clostridium difficile* infection in the United States. N Engl J Med. 2015 Feb 26;372(9): 825-834. doi: 10.1056/NEJMoa1408913

16. Figueroa I, Johnson S, Sambol SP, Goldstein EJC, Citron DM, Gerding DN. Relapse versus reinfection: recurrent *Clostridium difficile* infection following treatment with fidaxomicin or vancomycin. Clin Infect Dis. 2012;55(Suppl 2): S104–109.

17. Wheaton WD, Cajka JC, Chasteen BM, Wagener DK, Cooley PC, Ganapathi L, et al. Synthesized population databases: a US geospatial database for agent-based models. Methods Rep RTI Press. 2009 May 1;2009(10): 905. doi: 10.3768/rtipress.2009.mr.0010.0905

18. Cecil G. Sheps Center for Health Services Research, University of North Carolina at Chapel Hill. Short term acute care hospital discharge data - patient characteristics. Summary data for all hospitals. 2015 [cited January 28 2018]. Chapel Hill, NC: Cecil G. Sheps Center for Health Services Research,, University of North Carolina at Chapel Hill. Available: <http://www.shepscenter.unc.edu/wp-content/uploads/2013/05/ptchar_all_and_by_hos_2015.pdf>.

19. Centers for Medicare & Medicaid Services. Nursing home data compendium 2015 edition. Baltimore, MD: Centers for Medicare & Medicaid Services (CMS); 2015.

20. Kahn JM, Barnato AE, Lave JR, Pike F, Weissfeld LA, Le TQ, et al. A comparison of free-standing versus co-located long-term acute care hospitals. PLoS One. 2015;10(10): e0139742. doi: 10.1371/journal.pone.0139742

21. MedPac (2016) Report to the Congress. . Medicare Payment Policy. Washington, DC: The Medicare Payment Advisory Commission (MedPAC). pp. 288.

22. NC Department of Health and Human Services. North Carolina Health Statistics Pocket Guide. 2015 February 28, 2017 [cited January 21 2019]. Raleigh, NC: NC Division of Public Health. Available: <https://schs.dph.ncdhhs.gov/data/pocketguide/2015/>.

23. Deming WE, Stephan FF. On a least squares adjustment of a sampled frequency table when the expected marginal totals are known. Annals of Mathematical Statistics. 1940;11: 427-444.

24. Lang JB, Agresti A. Simultaneously modeling joint and marginal distributions of multivariate categorical responses. Journal of the American Statistical Association. 1994;89: 625-632.

25. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. JAMA. 1983 Apr 1;249(13): 1743-1745.

26. Centers for Disease Control and Prevention. Healthcare-associated infections - community interface (HAIC). 2016 annual report. January 2 [cited July 31 2019]. Atlanta, GA: CDC. Available: <https://www.cdc.gov/hai/eip/Annual-CDI-Report-2016.html>.

27. Centers for Disease Control and Prevention. Healthcare-associated infections - community interface (HAIC). Clostridioides difficiile infection (CDI) tracking. January 2 [cited July 31 2019]. Atlanta, GA: CDC. Available: <https://www.cdc.gov/hai/eip/cdiff-tracking.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fhai%2Feip%2Fclostridium-difficile.html>.

28. Kutty PK, Woods CW, Sena AC, Benoit SR, Naggie S, Frederick J, et al. Risk factors for and estimated incidence of community-associated *Clostridium difficile* infection, North Carolina, USA. Emerg Infect Dis. 2010 Feb;16(2): 197-204. doi: 10.3201/eid1602.090953

29. Centers for Disease Control and Prevention. Multidrug-resistant organism & clostridioides difficile infection (MDRO/CDI) module. 2019 [cited July 31 2019]. Atlanta, GA: CDC. Available: <https://www.cdc.gov/nhsn/PDFs/pscManual/12pscMDRO_CDADcurrent.pdf>.

30. Slimings C, Riley TV. Antibiotics and hospital-acquired Clostridium difficile infection: update of systematic review and meta-analysis. J Antimicrob Chemother. 2014 Apr;69(4): 881-891. doi: 10.1093/jac/dkt477

31. Vardakas KZ, Trigkidis KK, Boukouvala E, Falagas ME. Clostridium difficile infection following systemic antibiotic administration in randomised controlled trials: a systematic review and meta-analysis. International journal of antimicrobial agents. 2016 Jul;48(1): 1-10. doi: 10.1016/j.ijantimicag.2016.03.008

32. Hicks LA, Bartoces MG, Roberts RM, Suda KJ, Hunkler RJ, Taylor TH, Jr., et al. US outpatient antibiotic prescribing variation according to geography, patient population, and provider specialty in 2011. Clin Infect Dis. 2015 May 1;60(9): 1308-1316. doi: 10.1093/cid/civ076

33. Fleming-Dutra KE, Hersh AL, Shapiro DJ, Bartoces M, Enns EA, File TM, Jr., et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010-2011. JAMA. 2016 May 3;315(17): 1864-1873. doi: 10.1001/jama.2016.4151

34. Thompson ND, LaPlace L, Epstein L, Thompson D, Dumyati G, Concannon C, et al. Prevalence of antimicrobial use and opportunities to improve prescribing practices in U.S. nursing homes. J Am Med Dir Assoc. 2016 Dec 1;17(12): 1151-1153. doi: 10.1016/j.jamda.2016.08.013

35. Lim CJ, Kong DC, Stuart RL. Reducing inappropriate antibiotic prescribing in the residential care setting: current perspectives. Clin Interv Aging. 2014;9: 165-177. doi: 10.2147/CIA.S46058

36. Daneman N, Gruneir A, Bronskill SE, Newman A, Fischer HD, Rochon PA, et al. Prolonged antibiotic treatment in long-term care: role of the prescriber. JAMA Intern Med. 2013 Apr 22;173(8): 673-682. doi: 10.1001/jamainternmed.2013.3029

37. Katz PR, Beam TR, Jr., Brand F, Boyce K. Antibiotic use in the nursing home. Physician practice patterns. Arch Intern Med. 1990 Jul;150(7): 1465-1468.

38. Loeb M, Simor AE, Landry L, Walter S, McArthur M, Duffy J, et al. Antibiotic use in Ontario facilities that provide chronic care. Journal of general internal medicine. 2001 Jun;16(6): 376-383. doi: 10.1046/j.1525-1497.2001.016006376.x

39. Mylotte JM. Measuring antibiotic use in a long-term care facility. Am J Infect Control. 1996 Jun;24(3): 174-179.

40. Mylotte JM. Antimicrobial prescribing in long-term care facilities: prospective evaluation of potential antimicrobial use and cost indicators. Am J Infect Control. 1999 Feb;27(1): 10-19.

41. Nicolle LE, Bentley DW, Garibaldi R, Neuhaus EG, Smith PW. Antimicrobial use in long-term-care facilities. SHEA Long-Term-Care Committee. Infect Control Hosp Epidemiol. 2000 Aug;21(8): 537-545. doi: 10.1086/501798

42. Pakyz AL, Dwyer LL. Prevalence of antimicrobial use among United States nursing home residents: results from a national survey. Infect Control Hosp Epidemiol. 2010 Jun;31(6): 661-662. doi: 10.1086/653072

43. Warren JW, Palumbo FB, Fitterman L, Speedie SM. Incidence and characteristics of antibiotic use in aged nursing home patients. Journal of the American Geriatrics Society. 1991 Oct;39(10): 963-972. doi: 10.1111/j.1532-5415.1991.tb04042.x

44. NC Department of Health and Human Services. Healthcare-associated infections (HAIs). Facts and figures. 2019 July 22 [cited July 31 2019]. Raleigh, NC: NC Department of Health and Human Services. Available: <https://epi.dph.ncdhhs.gov/cd/hai/figures.html>.

45. American Hospital Association, Health Research & Educational Trust. HRET HIIN measurement matters: NHSN CDI Surveillance Definition Review. 2018 [cited July 31 2019]. Chicago, IL: American Hospital Association and Health Research & Educational Trust. Available: <http://www.hret-hiin.org/Resources/cdi/18/measurement-matters-nhsn-cdi-surveillance-definition-review-slides.pd>.

46. Centers for Disease Control and Prevention. *C diff* FAQ. Frequently asked questions about *Clostridium difficile* for healthcare providers. 2018 December 17 [cited January 21 2019]. Atlanta, GA: Centers for Disease Control and Prevention. Available: <https://www.cdc.gov/hai/organisms/cdiff/cdiff_faqs_hcp.html>.