**Appendix**

*RHEA-OC Model*

In our previous work, we used our RHEA software[1] to generate an ABM of Orange County (OC), California, to simulate CRE transmission[2, 3]. This ABM included detailed representations of adult patients admitted to all 102 healthcare facilities serving adult patients, including 23 acute care hospitals, 5 long-term acute care facilities (LTACs), and 74 nursing homes, and their return to the community.

Briefly, the model represents each patient as a computational agent, which on a given day, can either carry or not carry CRE.[2] Each simulated day, agents move from the community or other healthcare facilities into the various healthcare facilities, each with its actual number of beds and wards, and draws a facility- and ward-specific LOS taken from actual facility data.[4, 5] Each patient could be either a CRE carrier or non-carrier. Each day, within each ward, patients mix homogeneously, and CRE carriers can transmit CRE to non-carriers, based on a ward- and facility-specific transmission coefficient (beta): β\*susceptible patients\*infectious CRE patients. Once the patient’s LOS elapses, the patient leaves the facility and has probabilities of returning to the community, directly transferring to another OC facility, or returning to the community for a period of time before being re-admitted to the same or another facility. Our model was calibrated to match CRE prevalence trends currently seen in OC facilities.[3]

*Clinical and Economic Model*

The number of incident CRE carriers each year from the RHEA model then entered the clinical and economic model. Appendix Table 1 shows the model input parameters, values, and sources. Details of this model have been previously published.[6] Briefly, each CRE colonized patient entering the model had a probability of developing a CRE infection (assumed a base case of 5%), with a probability of being one of four types: primary bacteremia, intra-abdominal infection, pneumonia, or complicated urinary tract infection (UTI). Those with pneumonia had a probability of ventilator-associated pneumonia (VAP). All patients, regardless of infection type, had probabilities of receiving different types of treatment: monotherapy, carbapenem-containing combination therapy or non-carbapenem containing combination therapy. Each patient had a probability of mortality, depending on their infection type, treatment received, and CRE’s attributable mortality (assumed a base case of 35%). All patients with a CRE infection were placed on contact precautions (i.e., gloves and gowns for each patient contact) for their infection-specific attributable LOS (Appendix Table 1), following the standard of care. Additional tests and procedures were infection-specific. We assumed all nursing home patients with active CRE infections would require hospitalization.

Likewise, the number of persons screened (based upon the CDC CRE Toolkit), CRE carriers screened (true positives and false negatives), CRE carriers identified by screening on contact precautions (true positives), and non-carriers misidentified by screening on contact precautions (false positive) entered the model. All patient screened incurred the cost of screening (swab, chromogenic agar materials, and technician wage for time to process the sample); those on contact precautions incurred the cost of gloves and gowns plus time to don/doff for each room entry for the duration of their LOS.

We estimated costs from the hospital, third party payer, and societal perspectives. The hospital perspective measured illness costs in lost bed days (i.e., additional LOS attributable to CRE infection) derived from the infection specific attributable LOS and cost per bed day plus intervention costs. This represents the opportunity cost of lost bed days following a method described by Graves.[7] The third party payer perspective included direct costs (e.g., intervention, hospitalization, drug treatments, and associated tests). The cost of hospitalization for each clinical outcomes came from the Healthcare Cost and Utilization Project (HCUP).[16] In the absence of a specific International Classification of Diseases, 9th Revision (ICD-9) diagnosis code for CRE, we attempted to capture those codes that CRE patients may get for each clinical outcomes. Thus, these costs may not capture all discharges for each general clinical outcome and may differ from other hospitalization of the same category that fall under a different code or may be less severe disease (e.g., bacterial pneumonia not otherwise specified is less costly than *Klebsiella pneumoniae* pneumonia, which we used). Additionally, some of these ICD-9 codes are associated with a small number of total discharges (ranging from 950 for VAP to 247,120 for UTI), which may underestimate the variability in hospitalization cost. The social perspective included direct and indirect (i.e., productivity losses due to absenteeism and attributable mortality) costs, where all persons, regardless of age, incurred productivity losses. Hourly wages for all occupations in the US[8] were used as a proxy for productivity losses. Productivity losses for mortality resulted in the net present value of missed lifetime earnings based on the yearly annual wage[8] and years of life lost based on that patient’s life expectancy[9]. All input parameters are age-specific when applicable and all past and future costs were discounted to 2017 $US using a 3% discount rate.

For each scenario, we calculated both its cost-benefit and incremental cost-effectiveness ratio (ICER), as follows:

Cost-Benefit = Benefit – Cost = Direct Cost and Productivity Losses of Averted Infections – Cost of Intervention

CostCRE control – CostBaseline

ICER = -----------------------------------------------------------------------

Health EffectsBaseline – Health EffectsCRE Control

where health effects were measured in quality-adjusted life years (QALYs). We calculated the QALYs lost due to CRE infection (i.e., accounting only for reductions in health effects due to illness and/or death). Each CRE infection case accrued QALY decrements based on their age-dependent healthy QALY value attenuated by the infection-specific utility weight for the duration of their infection. All future QALYs were discount to present year values using a 3% rate. Thus, death resulted in the loss of a person’s discounted lifetime QALY value for the remainder his/her life expectancy. ICERs were considered cost-effective with a $50,000/QALY saved threshold.

Appendix Table 1. Clinical and economic model input parameters, values, and sources

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | **Distribution Type** | **Mean or Median** | **Standard Deviation or Range** | **Source** |
| *Costs (2017 $US)* |  |  |  |  |
| Gloves (pair) | gamma | 0.11 | 0.01 | [10, 11] |
| Gown | - | 1.10 | - | [10] |
| Swab | - | 1 | - | [12] |
| Chromogenic agar materials | - | 4.70 | - | [13] |
| ICU bed day | gamma | 5,040 | 32.61 | [14, 15] |
| General ward bed day\*‡ | gamma | 2,963 | 26.19 | [16] |
| Hospitalization\*† |  |  |  |  |
| Bacteremia | gamma | 13,628 | 408 | [16] |
| Intra-abdominal infection | gamma | 15,009 | 286 | [16] |
| Pneumonia (non-VAP) | gamma | 21,597 | 1,899 | [16] |
| Ventilator-associated pneumonia (VAP) | gamma | 28,820 | 2,422 | [16] |
| Urinary tract infection (UTI) | gamma | 8,000 | 130 | [16] |
| Drug treatments per day†† |  |  |  |  |
| Tigecycline | - | 303.42 | - | [17] |
| Meropenem | - | 136.91 | - | [17] |
| Gentamicin | - | 46.02 | - | [17] |
| Amikacin | - | 61.22 | - | [17] |
| Colistin | - | 90.14 | - | [17] |
| PICC line insertion | - | 101.40 | - | [18] |
| Urine analysis | gamma | 3.10 | 0.14 | [19] |
| Urine culture | gamma | 11.02 | 1.11 | [19] |
| Abdominal CT scan | gamma | 268.50 | 79.10 | [18] |
| Bronchoscopy | gamma | 142.46 | 25.93 | [18] |
| Wound culture | gamma | 12.26 | 0.96 | [19] |
| Chest x-ray | - | 29.65 | - | [18] |
| Sputum cultures | gamma | 18.30 | 2.16 | [18] |
| Blood culture | gamma | 14.42 | 1.64 | [19] |
| Median hourly wage (all occupations) | gamma | 18.67 | 9.64 – 47.32^ | [8] |
| Median annual wage (all occupations) | gamma | 38,835.12 | 20,051.55 – 98,410.99^ | [8] |
| Registered nurse hourly wage | gamma | 35.01 | 24.10 – 51.95^ | [8] |
| Technician hourly wage | gamma | 19.87 | 13.21 – 31.01^ |  |
| *Probabilities (%)* |  |  |  |  |
| Primary bacteremia | - | 20.28 | - | [20-25] |
| Intra-abdominal infection | - | 5.92 | - | [20-25] |
| Pneumonia (VAP and non-VAP) | - | 25.70 | - | [20-25] |
| Ventilator-associated pneumonia (VAP) given CRE pneumonia | - | 5.76 | - | [20-25] |
| Urinary tract infection (UTI) | - | 48.09 | - | [20-25] |
| Probability of ICU at onset | beta | 44.2 | 4.53 | [22, 26] |
| Treatment probabilities |  |  |  |  |
| Monotherapy | - | 47.03 | - | [27, 28] |
| Carbapenem containing combination therapy | - | 38.86 | - | [27, 28] |
| Non-carbapenem containing combination therapy | - | 14.11 | - | [27, 28] |
| Mortality from bacteremia |  |  |  |  |
| Monotherapy | - | 46.4 | - | [28] |
| Carbapenem containing combination therapy | - | 40.7 | - | [28] |
| Non-carbapenem containing combination therapy | - | 18.2 | - | [28] |
| Mortality from intra-abdominal infection |  |  |  |  |
| Monotherapy | - | 33.3 | - | [28] |
| Carbapenem containing combination therapy | - | 31.4 | - | [28] |
| Non-carbapenem containing combination therapy | - | 0.0 | - | [28] |
| Mortality from pneumonia |  |  |  |  |
| Monotherapy | - | 46.7 | - | [28] |
| Carbapenem containing combination therapy | - | 30.4 | - | [28] |
| Non-carbapenem containing combination therapy | - | 27.8 | - | [28] |
| Mortality from urinary tract infection |  |  |  |  |
| Monotherapy | - | 38.9 | - | [28] |
| Carbapenem containing combination therapy | - | 28.6 | - | [28] |
| Non-carbapenem containing combination therapy | - | 10.0 | - | [28] |
| *Durations (days) and Numbers* |  |  |  |  |
| Attributable length of stay |  |  |  |  |
| Primary bacteremia | uniform |  | 9 – 10 | [21-23] |
| Intra-abdominal infection | uniform |  | 14 – 21 | Expert opinion |
| Pneumonia (non-VAP) | uniform |  | 4 – 10 | [30] |
| Ventilator-associated pneumonia (VAP) | uniform |  | 10 – 14 | [31-35] |
| Urinary tract infection (UTI) | uniform |  | 4 – 8 | [36] |
| Treatment durations |  |  |  |  |
| Primary bacteremia | - | 14 | - | [37], Expert opinion |
| Intra-abdominal infection | uniform |  | 10 – 14 | [37], Expert opinion |
| Pneumonia (non-VAP) | uniform |  | 10 – 14 | [37], Expert opinion |
| Ventilator-associated pneumonia (VAP) | - | 14 | - | [37], Expert opinion |
| Urinary tract infection (UTI) | uniform |  | 14 – 21 | [37], Expert opinion |
| Patient contacts per day | uniform |  | 25 – 50 | [38] |
| Technician time to process sample (minutes) | - | 3.5 | - | [12] |
| Weight (kg) adults ≥60 years | beta pert | 78.35 | 64.8 – 90.5 | [39] |
| Baseline QALY value | - | 0.84 | - |  |
| Utility Weights |  |  |  |  |
| Primary bacteremia | beta | 0.985 | 0.015 | [40-44] |
| Intra-abdominal infection | beta | 0.518 | 0.179 | [45-50] |
| Pneumonia (non-VAP) | beta | 0.969 | 0.046 | [40, 42, 51, 52] |
| Ventilator-associated pneumonia (VAP) | beta | 0.875 | 0.064 | [53] |
| Urinary tract infection (UTI) | beta | 0.807 | 0.086 | [45, 54-56] |

\*Values are weighted mean for those aged 45-64 years and 65-84 years

‡Estimated for all non-neonatal, non-material discharges

†Estimated using the following International Classification of Diseases, 9th Revision (ICD-9) codes: 790.7 for bacteremia; 540.0 for intra-abdominal infection; 482.0 for pneumonia (non-VAP); 997.31 for ventilator-associated pneumonia; and 599.0 for urinary tract infection

^Values are 10% to 90% range

††Drug treatments followed Micromedex refined by expert opinion

Appendix Table 2. Breakdown of cumulative median costs for CRE control strategies over time (assuming base case with 5% probability of infection and 35% attributable mortality). Sum is total cost from societal perspective, while intervention costs plus direct costs is total cost from third party payer perspective

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Year Since Initial Introduction of CRE into Orange County, CA** | | | | | | | | | |
|  | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
| **Cumulative Intervention Costs** | | | | | | | | | | |
| Routine Control Measures | - | - | - | - | - | - | - | - | - | - |
| Uncoordinated, trigger of 1 | 48,146 | 402,627 | 1,096,165 | 1,951,358 | 2,871,795 | 3,810,948 | 4,750,315 | 5,684,636 | 6,613,442 | 7,530,240 |
| Uncoordinated, trigger of 10 | 2,199 | 23,423 | 77,761 | 219,747 | 562,189 | 1,110,608 | 1,810,039 | 2,618,411 | 3,495,801 | 4,409,179 |
| Uncoordinated, trigger of 20 | 202 | 10,368 | 39,715 | 99,261 | 219,630 | 489,562 | 949,546 | 1,562,938 | 2,293,774 | 3,107,473 |
| Coordinated, trigger of 1 | 845,581 | 1,874,658 | 2,903,102 | 3,906,056 | 4,886,822 | 5,847,455 | 6,793,149 | 7,725,128 | 8,643,841 | 9,545,867 |
| Coordinated, trigger of 10 | 7,716 | 668,962 | 1,715,652 | 2,740,547 | 3,744,766 | 4,729,596 | 5,700,828 | 6,660,223 | 7,606,875 | 8,540,242 |
| Coordinated, trigger of 20 | - | 69,938 | 816,997 | 1,850,718 | 2,878,156 | 3,888,142 | 4,884,004 | 5,867,436 | 6,837,026 | 7,794,857 |
| **Cumulative Direct Costs** | | | | | | | | | | |
| Routine Control Measures | 114,979 | 493,198 | 1,065,988 | 1,900,640 | 2,993,333 | 4,325,140 | 5,872,716 | 7,601,161 | 9,467,766 | 11,435,070 |
| Uncoordinated, trigger of 1 | 84,454 | 276,668 | 515,498 | 823,830 | 1,205,089 | 1,664,468 | 2,210,326 | 2,847,204 | 3,576,182 | 4,403,357 |
| Uncoordinated, trigger of 10 | 111,654 | 392,812 | 725,786 | 1,153,436 | 1,704,497 | 2,390,707 | 3,215,138 | 4,176,953 | 5,263,367 | 6,463,212 |
| Uncoordinated, trigger of 20 | 114,892 | 446,242 | 850,631 | 1,359,880 | 1,982,294 | 2,753,222 | 3,691,919 | 4,789,862 | 6,033,248 | 7,406,285 |
| Coordinated, trigger of 1 | 101,540 | 278,557 | 482,593 | 742,243 | 1,066,195 | 1,460,067 | 1,926,891 | 2,474,896 | 3,107,806 | 3,834,507 |
| Coordinated, trigger of 10 | 116,678 | 477,514 | 829,321 | 1,225,910 | 1,693,469 | 2,244,897 | 2,889,266 | 3,636,246 | 4,487,786 | 5,441,718 |
| Coordinated, trigger of 20 | 115,513 | 508,621 | 1,065,123 | 1,660,131 | 2,306,115 | 3,038,986 | 3,877,628 | 4,835,569 | 5,904,790 | 7,081,576 |
| **Cumulative Productivity Losses** | | | | | | | | | | |
| Routine Control Measures | 404,343 | 1,546,373 | 3,563,307 | 6,502,322 | 10,349,964 | 15,039,587 | 20,488,987 | 26,575,269 | 33,148,045 | 40,075,411 |
| Uncoordinated, trigger of 1 | 315,004 | 937,447 | 1,848,756 | 3,022,740 | 4,471,260 | 6,212,470 | 8,279,776 | 10,700,785 | 13,487,919 | 16,643,521 |
| Uncoordinated, trigger of 10 | 408,196 | 1,280,565 | 2,468,120 | 3,994,511 | 5,953,015 | 8,420,384 | 11,381,219 | 14,831,322 | 18,739,528 | 23,052,061 |
| Uncoordinated, trigger of 20 | 429,127 | 1,487,331 | 2,984,873 | 4,863,607 | 7,148,566 | 9,963,194 | 13,406,804 | 17,450,944 | 22,050,249 | 27,158,683 |
| Coordinated, trigger of 1 | 338,241 | 853,487 | 1,547,532 | 2,421,623 | 3,507,762 | 4,825,700 | 6,394,132 | 8,244,255 | 10,389,101 | 12,834,873 |
| Coordinated, trigger of 10 | 411,123 | 1,522,840 | 2,825,048 | 4,277,864 | 5,984,655 | 7,987,502 | 10,329,962 | 13,041,929 | 16,123,954 | 19,570,982 |
| Coordinated, trigger of 20 | 413,377 | 1,607,574 | 3,628,594 | 5,799,777 | 8,161,592 | 10,843,437 | 13,910,886 | 17,387,386 | 21,261,538 | 25,522,997 |

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