

**Final report for the technology evaluation of cefiderocol for treating severe aerobic Gram-negative bacterial infections**

**28th January 2022**



EEPRU model errors

An error in the EEPRU model relating to the long-term survival with acute kidney injury (AKI) and chronic kidney disease (CKD) impacted the long-term costs, and life year (LY) and quality-adjusted life year (QALY) gains for all comparators in the evaluation of cefiderocol. Two further errors were identified by Shionogi, detailed in their consultee comments. This addendum outlines the impact of the errors on the model results.

Summary of results

The impact of model errors identified by Shionogi was detailed in the EEPRU’s documented responses to key consultee comments. In short, rectifying the errors had the following impact.

* No impact on expected outcomes in the base-case model.
* Negligible impact on uncertainty in patient-level incremental net health benefit (INHE) in the empiric setting.
* Decrease in the patient-level benefit of cefiderocol in the scenario with higher costs of long-term care.

Correcting the additional error relating to the long-term survival with AKI and CKD increased the patient level INHE in all scenarios. The changes in the base-case results are summarised in Table 1. In the scenario analyses in the empiric setting (ES) (Table 4 and Table 6 in Sections 2.1 and 2.3), after correcting the error, three scenarios (applying a range of alternative assumptions to model the long-term effects of AKI, and using alternative sources to inform baseline mortality and mortality associated with nephrotoxicity) no longer modified the deterministic base-case by more than 10% in hospital-acquired pneumonia or ventilator-associated pneumonia (HAP/VAP) caused by carbapenemase-producine *Enterobacterales* (CPEs). In the scenario analyses in the microbiology directed setting (MDS) (Table 8 and Table 10 in Sections 2.2 and 2.4), the scenarios that modified the deterministic base-case by more than 10% altered as follows:

* Using alternative sources to inform the probability of AKI with colistin/aminoglycoside therapy modified the deterministic base-case by more than 10% for infections caused by *Enterobacterales* (HAP/VAP and complicated urinary tract infections, cUTI).
* Two scenarios (applying a range of alternative assumptions to model the long-term effects of AKI and using alternative sources to inform mortality associated with nephrotoxicity) no longer modified the deterministic base-case by more than 10% in HAP/VAP infections (for both pathogens).
* Fitting loglogistic distribution to data predicting long term outcomes modified the deterministic base-case by more than 10% for all pathogens and sites of infection, while in the report it only impacted HAP/VAP indections caused by *Enterobacterales*.

Table 1. Base-case patient-level INHE (probabilistic, 2,000 simulations) in the EEPRU report and post-correction. (Update of Tables 34, 36, 38 and 40 in EEPRU report)

|  |  |  |  |
| --- | --- | --- | --- |
| Pathogen | Site and setting | INHE (QALYs) in EEPRU report (Table 34, 36, 38 and 40 in EEPRU report) | INHE (QALYs) corrected (Tables 3, 5, 7 and 9 in Addendum 2) |
| *Enterobacterales* | HAP/VAP ES, ca | 0.118 (Table 34) | 0.147 (Table 3) |
| HAP/VAP MDS | 0.019 (Table 36) | 0.021 (Table 5) |
| cUTI MDS | 0.018 (Table 36) | 0.021 (Table 5) |
| *Pseudomonas* *aeruginosa* | HAP/VAP ES, nca | 0.149 (Table 38) | 0.153 (Table 7) |
| HAP/VAP ES, ca | 0.176 (Table 38) | 0.207 (Table 7) |
| HAP/VAP MDS | 0.127 (Table 40) | 0.151 (Table 9) |
| cUTI MDS | 0.104 (Table 40) | 0.147 (Table 9) |

ca, colistin/aminoglycoside therapy; cUTI, complicated urinary tract infections; ES, empiric setting; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia; INHE, incremental net health effect; MDS, microbiology-directed setting; nca, non-colistin/aminoglycoside therapy; QALYs, quality-adjusted life years

When the corrected patient-level INHE was extrapoalted to the population, the total population-level INHE increased, as shown in Table 2. The impact of the error changed the total population-level INHE from between 710 and 2,994 QALYs in the EEPRU report to between 896 and 3,559 post corrections, where ranges represent the mean INHE based on different assumptions about the population size (scenarios P1G1 and P2G2 in the EEPRU report). The impact of the error on the population-level results was the highest in HAP/VAP infections caused by CPEs, reflecting both the large population size and the impact of the error on patient-level benefits.

In the population-level scenario analyses, four scenarios that modified the deterministic base-case INHE by more than 10% in the EEPRU report no longer impacted the results by that degree: adjustment of baseline mortality from the CARBAR study to remove the impact of AKIs, doubling the risk of CKD to reflect potential higher propensity for CKD in this patient population, applying a range of alternative assumptions to model the long-term effects of AKI, and adding the cost of long-term care. The reduced impact of these scenarios reflects their reduced impact on patient-level benefit in HAP/VAP (and bloodstream infections, BSI) that represents the majority of infections overall.

Table 2. Base-case population-level INHE (deterministic) in the EEPRU report and post-correction. Ranges represent different assumptions about the population size (scenarios P1G1 and P2G2 in the EEPRU report). (Update of Table 36 in EEPRU report)

|  |  |  |  |
| --- | --- | --- | --- |
| Pathogen |  | INHE (QALYs) in EEPRU report (Table 42 in EEPRU report) | INHE (QALYs) corrected(Table 11 in Addendum 2) |
| CPE, MBL | HAP/VAP ES | 62 – 775 | 80 – 959 |
| cUTI MDS | 22 – 59 | 25 – 68 |
| BSI ES | 379 – 764 | 495 – 945 |
| IAI MDS | 18 – 36 | 21 – 42 |
| *Pseudomonas* *aeruginosa*, MBL | HAP/VAP ES | 10 – 185 | 10 – 185 |
| cUTI MDS | 16 – 31 | 22 – 43 |
| BSI ES | 23 – 28 | 23 – 28  |
| IAI MDS | 19 – 22 | 26 – 30 |
| Stenotrophomonas | HAP/VAP MDS | 38 – 925 | 41 – 1,059 |
| cUTI MDS | 35 – 80 | 43 – 102 |
| BSI MDS | 40 – 72 | 44 – 80 |
| IAI MDS | 18 – 36 | 34 – 58 |
| Total | 710 – 2,994 | 896 – 3,559 |

BSI, bloodstream infections, cUTI, complicated urinary tract infections; ES, empiric setting; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia; IAI, intra-abdominal infections; INHE, incremental net health effect; MDS, microbiology-directed setting; nca, non-colistin/aminoglycoside therapy; QALYs, quality-adjusted life years

P1G1: baseline population (point estimate) based on PHE categorisation of infection sites, growth rate damped; P2G2: baseline population (point estimate) based on clinical advisors’ categorisation of infection sites, growth rate not damped.

The updated tables for all patient-level and population-level net health effects (NHE) in the high value clinical scenarios (HVCS) are presented below.

Updated figures and tables: patient-level outcomes

MBL *Enterobacterales*: base-case results in the ES

Table 3: Patient-level base-case results: MBL *Pseudomonas aeruginosa* HAP/VAP empiric setting (probabilistic, 2,000 simulations). (Update of Table 34 in EEPRU report)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **E1** | **E2ca** | **E3ca** | **E1-E2ca** | **E1-E3ca** |
| **Patients with MBL *Enterobacterales*** |
| ***Summary of in-hospital outcomes (proportions) across both lines of treatment available*** |
| Death | 0.399 | 0.403 | 0.403 | -0.004 | -0.003 |
| Survival no AKI | 0.473 | 0.428 | 0.428 | 0.046 | 0.045 |
| Survival AKI | 0.127 | 0.169 | 0.169 | -0.042 | -0.042 |
| Survival CKD | 0.000 | 0.000 | 0.001 | 0 | 0 |
| ***Economic outcomes (all discounted)*** |
| Treatment costs | £101 | £179 | £178 | -£78 | -£77 |
| AKI costs hospital | £1,954 | £2,285 | £2,283 | -£331 | -£329 |
| Other costs hospital | £21,301 | £16,319 | £16,301 | £4,982 | £5,000 |
| Long-term costs | £566 | £569 | £570 | -£3 | -£4 |
| Total costs | £23,922 | £19,352 | £19,331 | £4,570 | £4,591 |
| Life years | 2.58 | 2.52 | 2.52 | 0.06 | 0.06 |
| QALYs | 1.81 | 1.77 | 1.77 | 0.04 | 0.04 |
| Per person NHE | 0.615 | 0.803 | 0.806 | -0.188 | -0.191 |
| **Patients without MBL *Enterobacterales*** |
| ***Summary of in-hospital outcomes (proportions) across both lines of treatment available*** |
| Death | 0.351 | 0.403 | 0.403 | -0.052 | -0.052 |
| Survival no AKI | 0.524 | 0.428 | 0.428 | 0.096 | 0.096 |
| Survival AKI | 0.125 | 0.169 | 0.169 | -0.044 | -0.044 |
| Survival CKD | 0.000 | 0.000 | 0.000 | 0 | 0 |
| ***Economic outcomes (all discounted)*** |
| Treatment costs | £30 | £179 | £179 | -£149 | -£149 |
| AKI costs hospital | £1,672 | £2,285 | £2,285 | -£612 | -£612 |
| Other costs hospital | £16,736 | £16,319 | £16,319 | £417 | £417 |
| Long-term costs | £609 | £569 | £569 | £40 | £40 |
| Total costs | £19,048 | £19,352 | £19,352 | -£304 | -£304 |
| Life years | 2.80 | 2.52 | 2.52 | 0.28 | 0.28 |
| QALYs | 1.97 | 1.77 | 1.77 | 0.19 | 0.19 |
| Per person NHE | 1.013 | 0.803 | 0.803 | 0.209 | 0.209 |
| **All patients presenting in the ES** |
| Total costs | £19,800 | £19,352 | £19,349 | £447 | £451 |
| QALYs | 1.94 | 1.77 | 1.77 | 0.17 | 0.17 |
| Per person NHE | 0.952 | 0.803 | 0.803 | 0.148 | 0.147 |

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; ES, empiric setting; MBL, metallo-beta-lactamases; MDS, microbiology-directed setting; NHE, net health effect; QALYs, quality-adjusted life years

Comparators: E1 = empiric treatment with cefiderocol, followed by existing therapies in MDS if not susceptible; E2ca = colistin or aminoglycoside-based empiric treatment, followed by existing therapies MDS if needed; E3ca = colistin or aminoglycoside-based empiric treatment, followed by cefiderocol MDS if needed. Net health effects derived using threshold of £20,000/QALY.

Figure 1: Distribution of patient-level INHEs of cefiderocol compared to colistin/aminoglycoside-based therapy: MBL *Enterobacterales* HAP/VAP empiric setting (2,000 simulations) (Update of Figure 16 in EEPRU report)



NHE, net health effects

Table 4: Per patient scenario analyses: MBL *Enterobacterales* empiric setting (deterministic) (Update of Table 35 in EEPRU report)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Scenario name | Base-case value/assumption | Scenario value/assumption | Optimal cefiderocol use | Patient-level INHE of Cefiderocol  |
| Base-case | - | - | Empiric (E1) | 0.168 |
| p\_bug\_survey | Probability patient has MBL *Enterobacterales* is 0.15 | Probability patient has MBL *Enterobacterales* is 0.71 based on BSAC survey data | Reserve for use in MDS (E3ca) | 0.002 |
| p\_bug\_0 | Probability patient has MBL *Enterobacterales* is 0.15 | Probability patient has MBL *Enterobacterales* is 0.00 | Empiric (E1) | 0.228 |
| p\_bug\_10 | Probability patient has MBL *Enterobacterales* is 0.15 | Probability patient has MBL *Enterobacterales* is 0.10 | Empiric (E1) | 0.189 |
| p\_bug\_20 | Probability patient has MBL *Enterobacterales* is 0.15 | Probability patient has MBL *Enterobacterales* is 0.20 | Empiric (E1) | 0.150 |
| p\_bug\_30 | Probability patient has MBL *Enterobacterales* is 0.15 | Probability patient has MBL *Enterobacterales* is 0.30 | Empiric (E1) | 0.111 |
| p\_bug\_40 | Probability patient has MBL *Enterobacterales* is 0.15 | Probability patient has MBL *Enterobacterales* is 0.40 | Empiric (E1) | 0.072 |
| p\_bug\_50 | Probability patient has MBL *Enterobacterales* is 0.15 | Probability patient has MBL *Enterobacterales* is 0.50 | Empiric (E1) | 0.033 |
| p\_bug\_60 | Probability patient has MBL *Enterobacterales* is 0.15 | Probability patient has MBL *Enterobacterales* is 0.60 | Reserve for use in MDS (E3ca) | 0.002 |
| p\_bug\_70 | Probability patient has MBL *Enterobacterales* is 0.15 | Probability patient has MBL *Enterobacterales* is 0.70 | Reserve for use in MDS (E3ca) | 0.002 |
| p\_bug\_80 | Probability patient has MBL *Enterobacterales* is 0.15 | Probability patient has MBL *Enterobacterales* is 0.80 | Reserve for use in MDS (E3ca) | 0.002 |
| p\_bug\_90 | Probability patient has MBL *Enterobacterales* is 0.15 | Probability patient has MBL *Enterobacterales* is 0.90 | Reserve for use in MDS (E3ca) | 0.003 |
| p\_bug\_100 | Probability patient has MBL *Enterobacterales* is 0.15 | Probability patient has MBL *Enterobacterales* is 1.00 | Reserve for use in MDS (E3ca) | 0.003 |
| S1 | Susceptibility based on NMA of EUCAST studies | Susceptibility based on NMA of CLSI studies | Empiric (E1) | 0.208 |
| S3 | Susceptibility based on NMA of EUCAST studies | PHE data, with cefiderocol and fosfomycin data from separatecefiderocol and fosfomycin networks (CLSI studies) | Empiric (E1) | 0.229 |
| p\_AKI\_Chien | Probability of AKI with colistin/aminoglycoside therapy based on Sisay 2021 (0.45) | Probability of AKI with colistin/aminoglycoside therapy based on Chien (0.32) | Empiric (E1) | 0.128 |
| OR\_AKI\_Wagenlehner | Odds ratio comparing AKI for colistin/ aminoglycoside-based therapy to non-colistin/aminoglycoside-based therapy from all studies analysis in Chien 2020 (1.81) | Odds ratio comparing AKI for colistin/ aminoglycoside-based therapy to non-colistin/aminoglycoside-based therapy from all studies analysis in Wagenlehner 2021 (2.23) | Empiric (E1) | 0.234 |
| OR\_AKI\_ChienRIFLE | Odds ratio comparing AKI for colistin/ aminoglycoside-based therapy to non-colistin/aminoglycoside-based therapy from all studies analysis in Chien 2020 (1.81) | Odds ratio comparing AKI for colistin/ aminoglycoside-based therapy to non-colistin/aminoglycoside-based therapy from RIFLE criteria studies analysis in Chien 2020 (1.61) | Empiric (E1) | 0.128 |
| OR\_AKI\_death\_halved | Odds ratio of mortality for AKI compared to no AKI derived from Kerr (2014) (5.11) | Odds ratio of mortality for AKI compared to no AKI halved (2.56) | Empiric (E1) | 0.124 |
| double.ckd.risk | Risk of CKD as observed in Bucaloiu 2012 | Risk of CKD doubled to reflect potential higher propensity for CKD in HVCS | Empiric (E1) | 0.136 |
| abs.increase | Odds ratios on mortality associated with nephrotoxicity from Bucaloiu 2012 are applied multiplicatively to underlying risk in HVCS | Absolute risk increases in Bucaloiu 2012 are assumed to apply | Empiric (E1) | Change <10% relative to base case\* |
| all.aki.lt | Base case assumptions with respect to long-term effects of AKI | Applying a range of alternative assumptions to model the long-term effects of AKI | Empiric (E1) | Change <10% relative to base case\* |
| reduce.carbar | CARBAR unadjusted baseline mortality | CARBAR adjusted to remove impact of AKIs | Empiric (E1) | Change <10% relative to base case\* |
| loglogistic | Log-normal model fit to CARBAR survival data | Log-logistic model fit to CARBAR survival data | Empiric (E1) | 0.136 |
| weibull | Log-normal model fit to CARBAR survival data | Weibull model fit to CARBAR survival data | Empiric (E1) | 0.095 |
| lt.care | No costs of long-term care | Costs of discharge to long-term care  | Empiric (E1) | 0.174 |
| thresh15\* | Cost-effectiveness threshold £20,000 | Cost-effectiveness threshold £15,000 | Empiric (E1) | 0.159 |
| thresh30\* | Cost-effectiveness threshold £20,000 | Cost-effectiveness threshold £30,000 | Empiric (E1) | 0.176 |
| dr1.5\* | Discount rate for costs and benefits 3.5% | Discount rate for costs and benefits 1.5% | Empiric (E1) | 0.196 |

\* Scenarios that modified the base case INHE by more than 10% in the report but not after correcting the model errors.

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; CLSI, Clinical Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; HVCS, high value clinical scenario; INHE, incremental net health effects; MBL, metallo-beta-lactamases; NMA, network meta-analysis; Public Health England; RIFLE, risk, injury, failure, loss and end-stage renal disease

Comparators: E1 = empiric treatment with cefiderocol, followed by existing therapies in MDS if not susceptible; E3ca = colistin or aminoglycoside-based empiric treatment, followed by cefiderocol MDS if needed.

NB:Net health effects derived using cost-effectiveness threshold of £20,000/QALY.

MBL *Enterobacterales*: basecase results in the MDS

Table 5: Patient-level base-case results: MBL *Pseudomonas aeruginosa* HAP/VAP and cUTI microbiology-directed setting (probabilistic, 2,000 simulations) (Update of Table 36 in EEPRU report)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **MDS pathway with cefiderocol** | **MDS pathway without cefiderocol** | **Incremental values**  |
| **HAP/VAP** |
| ***Summary of in-hospital outcomes (proportions)*** |
| Death | 0.374 | 0.378 | -0.004 |
| Survival no AKI | 0.496 | 0.49 | 0.007 |
| Survival AKI | 0.129 | 0.132 | -0.002 |
| Survival CKD | 0 | 0 | 0 |
| ***Economic outcomes (all discounted)*** |
| Treatment costs | £280 | £295 | £-15 |
| AKI costs hospital | £1,673 | £1,712 | £-39 |
| Other costs hospital | £34,755 | £34,822 | £-67 |
| Long-term costs | £590 | £587 | £3 |
| Total costs | £37,297 | £37,415 | £-117 |
| Life years | 2.69 | 2.67 | 0.02 |
| QALYs | 1.89 | 1.87 | 0.02 |
| Per person NHE | 0.024 | 0.003 | 0.021 |
| **cUTI** |
| ***Summary of in-hospital outcomes (proportions)*** |
| Death | 0.126 | 0.13 | -0.004 |
| Survival no AKI | 0.646 | 0.638 | 0.008 |
| Survival AKI | 0.228 | 0.232 | -0.004 |
| Survival CKD | 0 | 0 | 0 |
| ***Economic outcomes (all discounted)*** |
| Treatment costs | £280 | £295 | -£15 |
| AKI costs hospital | £1,673 | £1,712 | -£39 |
| Other costs hospital | £17,370 | £17,427 | -£57 |
| Long-term costs | £830 | £827 | £3 |
| Total costs | £20,152 | £20,261 | -£108 |
| Life years | 3.71 | 3.69 | 0.02 |
| QALYs | 2.61 | 2.59 | 0.02 |
| Per person NHE | 1.599 | 1.579 | 0.021 |

AKI, acute kidney injury; CKD, chronic kidney disease; cUTI, complicated urinary tract infections; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia; MBL, metallo-beta-lactamases; MDS, microbiology-directed setting; NHE, net health effect; QALYs, quality-adjusted life years

Figure 2: Distribution of patient-level INHEs of introducing cefiderocol in to the MDS compared to existing therapies: (a) MBL *Enterobacterales* HAP/VAP and (b) MBL *Enterobacterales* cUTI (2,000 simulations) (Update of Figure 17 in EEPRU report)

1. **HAP/VAP (b) cUTI**

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MDS, microbiology-directed setting; NHE, net health effects

Table 6: Patient-level scenario analyses: MBL *Enterobacterales* HAP/VAP and cUTI MDS (deterministic). (Update of Table 37 in EEPRU report)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Scenario name** | **Base-case value/assumption** | **Scenario value/assumption** | **Patient-level INHE of cefiderocol: HAP/VAP** | **Patient-level INHE of cefiderocol: cUTI** |
| Base case | - | - | 0.023 | 0.022 |
| S1 | Susceptibility based on NMA of EUCAST studies | Susceptibility based on NMA of CLSI studies | 0.011 | 0.011 |
| S3 | Susceptibility based on NMA of EUCAST studies | PHE data, with cefiderocol and fosfomycin data from separatecefiderocol and fosfomycin networks (CLSI studies) | 0.017 | 0.017 |
| S4 | Susceptibility based on NMA of EUCAST studies | PHE data (cefiderocol from EUCAST NMA, excludes fosfomycin) | 0.056 | 0.056 |
| p\_AKI\_Chien | Probability of AKI with colistin/aminoglycoside therapy based on Sisay 2021 (0.45) | Probability of AKI with colistin/aminoglycoside therapy based on Chien (0.32) | 0.020\* | 0.020\* |
| OR\_AKI\_Wagenlehner | Odds ratio comparing AKI for colistin/ aminoglycoside-based therapy to non-colistin/aminoglycoside-based therapy from all studies analysis in Chien 2020 (1.81) | Odds ratio comparing AKI for colistin/ aminoglycoside-based therapy to non-colistin/aminoglycoside-based therapy from all studies analysis in Wagenlehner 2021 (2.23) | 0.027 | 0.027 |
| OR\_AKI\_ChienRIFLE | Odds ratio comparing AKI for colistin/ aminoglycoside-based therapy to non-colistin/aminoglycoside-based therapy from all studies analysis in Chien 2020 (1.81) | Odds ratio comparing AKI for colistin/ aminoglycoside-based therapy to non-colistin/aminoglycoside-based therapy from RIFLE criteria studies analysis in Chien 2020 (1.61) | 0.020 | 0.020\* |
| OR\_AKI\_death\_halved | Odds ratio of mortality for AKI compared to no AKI derived from Kerr (2014) (5.11) | Odds ratio of mortality for AKI compared to no AKI halved (2.56) | 0.019 | 0.019 |
| double.ckd.risk | Risk of CKD as observed in Bucaloiu 2012 | Risk of CKD doubled to reflect potential higher propensity for CKD in HVCS | 0.020 | 0.020 |
| abs.increase | Odds ratios on mortality associated with nephrotoxicity from Bucaloiu 2012 are applied multiplicatively to underlying risk in HVCS | Absolute risk increases in Bucaloiu 2012 are assumed to apply | Change <10% relative to base case\* | 0.023 |
| all.aki.lt | Base case assumptions with respect to long-term effects of AKI | Applying a range of alternative assumptions to model the long-term effects of AKI | Change <10% relative to base case\* | 0.023 |
| loglogistic | Log-normal model fit to CARBAR survival data | Log-logistic model fit to CARBAR survival data | 0.020 | 0.020\* |
| weibull | Log-normal model fit to CARBAR survival data | Weibull model fit to CARBAR survival data | 0.016 | 0.016 |
| lt.care | No costs of long-term care | Costs of discharge to long-term care  | Change <10% relative to base case | 0.023 |
| thresh15\* | Cost-effectiveness threshold £20,000 | Cost-effectiveness threshold £15,000 | 0.025 | 0.024 |
| thresh30\* | Cost-effectiveness threshold £20,000 | Cost-effectiveness threshold £30,000 | 0.020 | 0.021 |
| dr1.5\* | Discount rate for costs and benefits 3.5% | Discount rate for costs and benefits 1.5% | 0.025 | 0.025 |

AKI, acute kidney injury; CKD, chronic kidney disease; CLSI, Clinical Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; HVCS, high value clinical scenario; INHE, incremental net health effects; MBL, metallo-beta-lactamases; NMA, network meta-analysis; PHE, Public Health England; RIFLE, risk, injury, failure, loss and end-stage renal disease

NB:Net health effects derived using threshold of £20,000/QALY.

\* Scenarios that modified the base case INHE by more than 10% in the report but not after correcting the model errors, or vice versa.

MBL *Pseudomonas aeruginosa*: base-case results in the ES

Table 7: Patient-level base-case results: MBL *Pseudomonas aeruginosa* HAP/VAP empiric setting (probabilistic, 2,000 simulations). (Update of Table 38 in EEPRU report)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **E1** | **E2nca** | **E2ca** | **E3nca** | **E3ca** | **E1-E2nca****E2nca** | **E1-E2ca** |
| **Patients with MBL *Pseudomonas aeruginosa***  |
| ***Summary of in-hospital outcomes (proportions) across both lines of treatment available*** |
| Death | 0.352 | 0.496 | 0.401 | 0.459 | 0.397 | -0.143 | -0.048 |
| Survival no AKI | 0.522 | 0.362 | 0.43 | 0.404 | 0.432 | 0.161 | 0.092 |
| Survival AKI | 0.125 | 0.142 | 0.169 | 0.137 | 0.17 | -0.017 | -0.044 |
| Survival CKD | 0 | 0 | 0.001 | 0 | 0.001 | 0 | 0 |
| ***Economic outcomes (all discounted)*** |
| Treatment costs | £15 | £131 | £167 | £14 | £156 | -£116 | -£152 |
| AKI costs hospital | £1,684 | £2,607 | £2,270 | £2,315 | £2,255 | -£923 | -£586 |
| Other costs hospital | £16,599 | £28,276 | £15,930 | £27,331 | £15,795 | -£11,676 | £669 |
| Long-term costs | £608 | £481 | £571 | £514 | £575 | £127 | £37 |
| Total costs | £18,906 | £31,495 | £18,938 | £30,175 | £18,781 | -£12,589 | -£32 |
| Life years | 2.79 | 2.13 | 2.53 | 2.30 | 2.54 | 0.66 | 0.26 |
| QALYs | 1.96 | 1.50 | 1.78 | 1.62 | 1.79 | 0.47 | 0.18 |
| Per person NHE | 1.015 | -0.079 | 0.831 | 0.107 | 0.849 | 1.094 | 0.184 |
| **Patients without MBL *Pseudomonas aeruginosa*** |
| ***Summary of in-hospital outcomes (proportions) across both lines of treatment available*** |
| Death | 0.349 | 0.349 | 0.401 | 0.349 | 0.401 | 0 | -0.052 |
| Survival no AKI | 0.526 | 0.526 | 0.43 | 0.526 | 0.43 | 0 | 0.096 |
| Survival AKI | 0.125 | 0.125 | 0.169 | 0.125 | 0.169 | 0 | -0.044 |
| Survival CKD | 0 | 0 | 0.001 | 0 | 0.001 | 0 | 0 |
| ***Economic outcomes (all discounted)*** |
| Treatment costs | £12 | £22 | £167 | £22 | £167 | -£10 | -£155 |
| AKI costs hospital | £1,663 | £1,663 | £2,270 | £1,663 | £2,270 | £0 | -£608 |
| Other costs hospital | £16,313 | £16,313 | £15,930 | £16,313 | £15,930 | £0 | £383 |
| Long-term costs | £611 | £611 | £571 | £611 | £571 | £0 | £40 |
| Total costs | £18,599 | £18,609 | £18,938 | £18,609 | £18,938 | -£10 | -£339 |
| Life years | 2.81 | 2.81 | 2.53 | 2.81 | 2.53 | 0.00 | 0.28 |
| QALYs | 1.97 | 1.97 | 1.78 | 1.97 | 1.78 | 0.00 | 0.19 |
| Per person NHE | 1.042 | 1.041 | 0.831 | 1.041 | 0.831 | 0 | 0.211 |
| **All patients presenting in the ES** |
| Total costs | £18,642 | £20,412 | £18,938 | £20,228 | £18,916 | -£1,770 | -£296 |
| QALYs | 1.97 | 1.91 | 1.78 | 1.92 | 1.78 | 0.07 | 0.19 |
| Per person NHE | 1.038 | 0.884 | 0.831 | 0.910 | 0.834 | 0.153 | 0.207 |

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; MBL, metallo-beta-lactamases; MDS, microbiology-directed setting; NHE, net health effect; QALYs, quality-adjusted life years

Comparators: E1 = empiric treatment with cefiderocol, followed by existing therapies in MDS if not susceptible; E2nca = non-colistin or aminoglycoside-based empiric treatment, followed by existing therapies MDS if needed; E2ca = colistin or aminoglycoside-based empiric treatment, followed by existing therapies MDS if needed; E3nca = non-colistin or aminoglycoside-based empiric treatment, followed by followed by cefiderocol in MDS if needed; E3ca = colistin or aminoglycoside-based empiric treatment, followed by cefiderocol MDS if needed. Net health effects derived using threshold of £20,000/QALY.

**Figure 3: Distribution of patient-level INHEs of cefiderocol in MBL *Pseudomonas aeruginosa* HAP/VAP empiric setting compared to (a) non-colistin/aminoglycoside-based therapy and (b) colistin/aminoglycoside-based therapy and (2,000 simulations). (Update of Figure 18 in EEPRU report)**

1. **(b)**

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NHE, net health effects

Table 8: Patient-level scenario analyses: MBL *Pseudomonas aeruginosa* empiric setting (deterministic). (Update of Table 39 in EEPRU report)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Scenario name** | **Base-case value/assumption** | **Scenario value/assumption** | **Best existing treatment** | **Patient-level INHE of cefiderocol**  |
| Base-case | - | - | Non-colistin/amino-based | 0.145 |
| p\_bug\_survey | Probability patient has MBL *Pseudomonas aeruginosa* is 0.14 | Probability patient has MBL *Enterobacterales* is 0.71 based on BSAC survey data | Colistin/amino-based | 0.210 |
| p\_bug\_0 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.14 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.00 | Non-colistin/amino-based | 0.000 |
| p\_bug\_10 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.14 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.10 | Non-colistin/amino-based | 0.105 |
| p\_bug\_20 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.14 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.20 | Non-colistin/amino-based | 0.211 |
| p\_bug\_30 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.14 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.30 | Colistin/amino-based | 0.221 |
| p\_bug\_40 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.14 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.40 | Colistin/amino-based | 0.218 |
| p\_bug\_50 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.14 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.50 | Colistin/amino-based | 0.216 |
| p\_bug\_60 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.14 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.60 | Colistin/amino-based | 0.213 |
| p\_bug\_70 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.14 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.70 | Colistin/amino-based | 0.211 |
| p\_bug\_80 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.14 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.80 | Colistin/amino-based | 0.208 |
| p\_bug\_90 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.14 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.90 | Colistin/amino-based | 0.206 |
| p\_bug\_100 | Probability patient has MBL *Pseudomonas aeruginosa* is 0.14 | Probability patient has MBL *Pseudomonas aeruginosa* is 1.00 | Colistin/amino-based | 0.203 |
| S1 | Susceptibility based on NMA of EUCAST studies | Susceptibility based on NMA of CLSI studies | Non-colistin/amino-based | 0.026 |
| S3 | Susceptibility based on NMA of EUCAST studies | PHE data, with cefiderocol and fosfomycin data from separatecefiderocol and fosfomycin networks (CLSI studies). | Non-colistin/amino-based | 0.007 |
| weibull | Log-normal model fit to CARBAR survival data | Weibull model fit to CARBAR survival data | Non-colistin/amino-based | 0.123 |
| thresh15\* | Cost-effectiveness threshold £20,000 | Cost-effectiveness threshold £15,000 | Non-colistin/amino-based | 0.174 |
| thresh30\* | Cost-effectiveness threshold £20,000 | Cost-effectiveness threshold £30,000 | Non-colistin/amino-based | 0.117 |
| dr1.5\* | Discount rate for costs and benefits 3.5% | Discount rate for costs and benefits 1.5% | Non-colistin/amino-based | 0.154 |

AKI, acute kidney injury; CKD, chronic kidney disease; CLSI, Clinical Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; HVCS, high value clinical scenario; INHE, incremental net health effects; MBL, metallo-beta-lactamases; NMA, network meta-analysis; PHE, Public Health England

MBL *Pseudomonas aeruginosa*: base-case results in the MDS

Table 9: Patient-level base-case results: MBL *Pseudomonas aeruginosa* HAP/VAP and cUTI microbiology-directed setting (probabilistic, 2,000 simulations). (Update of Table 40 in EEPRU report)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **MDS pathway with cefiderocol** | **MDS pathway without cefiderocol** | **Incremental values**  |
| **HAP/VAP** |
| ***Summary of in-hospital outcomes (proportions)*** |
| Death | 0.373 | 0.404 | -0.031 |
| Survival no AKI | 0.497 | 0.431 | 0.066 |
| Survival AKI | 0.129 | 0.164 | -0.035 |
| Survival CKD | 0 | 0 | 0 |
| ***Economic outcomes (all discounted)*** |
| Treatment costs | £6 | £114 | -£108 |
| AKI costs hospital | £1,667 | £2,126 | -£459 |
| Other costs hospital | £34,724 | £34,755 | -£31 |
| Long-term costs | £591 | £568 | £23 |
| Total costs | £36,987 | £37,563 | -£576 |
| Life years | 2.69 | 2.52 | 0.18 |
| QALYs | 1.89 | 1.77 | 0.12 |
| Per person NHE | 0.043 | -0.108 | 0.151 |
| **cUTI** |
| ***Summary of in-hospital outcomes (proportions)*** |
| Death | 0.125 | 0.149 | -0.024 |
| Survival no AKI | 0.648 | 0.562 | 0.086 |
| Survival AKI | 0.228 | 0.289 | -0.062 |
| Survival CKD | 0 | 0 | 0 |
| ***Economic outcomes (all discounted)*** |
| Treatment costs | £6 | £114 | -£108 |
| AKI costs hospital | £1,667 | £2,126 | -£459 |
| Other costs hospital | £17,345 | £17,375 | -£30 |
| Long-term costs | £831 | £819 | £12 |
| Total costs | £19,848 | £20,434 | -£586 |
| Life years | 3.72 | 3.55 | 0.17 |
| QALYs | 2.61 | 2.49 | 0.12 |
| Per person NHE | 1.618 | 1.471 | 0.147 |

AKI, acute kidney injury; CKD, chronic kidney disease; cUTI, complicated urinary tract infections; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia; MBL, metallo-beta-lactamases; MDS, microbiology-directed setting; NHE, net health effect; QALYs, quality-adjusted life years

Figure 4: Distribution of INHEs of introducing cefiderocol in to the MDS compared to existing therapies: (a) MBL *Pseudomonas aeruginosa* HAP/VAP and (b) MBL *Pseudomonas aeruginosa* cUTI (2,000 simulations). (Update of Figure 19 in EEPRU report)

 **(a) HAP/VAP (b) cUTI**

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MDS, microbiology-directed setting; NHE, net health effects

Table 10: Patient-level scenario analyses: MBL *Pseudomonas aeruginosa* HAP/VAP and cUTI MDS (deterministic). (Update of Table 41 in EEPRU report)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Scenario name** | **Base-case value/assumption** | **Scenario value/assumption** | **Patient-level INHE of cefiderocol: HAP/VAP** | **Patient-level INHE of cefiderocol: cUTI** |
| Base case | - | - | 0.174 | 0.170 |
| S1 | Susceptibility based on NMA of EUCAST studies | Susceptibility based on NMA of CLSI studies | 0.035 | 0.034 |
| S3 | Susceptibility based on NMA of EUCAST studies | PHE data, with cefiderocol and fosfomycin data from separatecefiderocol and fosfomycin networks (CLSI studies). | 0.009 | 0.009 |
| S4 | Susceptibility based on NMA of EUCAST studies | NMA of EUCAST studies, absolute colistin susceptibility values from SIDERO WT | 0.253 | 0.254 |
| p\_AKI\_Chien | Probability of AKI with colistin/aminoglycoside therapy based on Sisay 2021 (0.45) | Probability of AKI with colistin/aminoglycoside therapy based on Chien (0.32) | 0.144 | 0.140 |
| OR\_AKI\_Wagenlehner | Odds ratio comparing colstin/aminoglycoside based therapy to non-colistin/aminoglycoside based therapy from all studies analysis in Chien 2020 (1.81) | Odds ratio comparing colstin/aminoglycoside based therapy to non-colistin/aminoglycoside based therapy from all studies analysis in Wagenlehner 2021 (2.23) | 0.224 | 0.218 |
| OR\_AKI\_ChienRIFLE | Odds ratio comparing colstin/aminoglycoside based therapy to non-colistin/aminoglycoside based therapy from all studies analysis in Chien 2020 (1.81) | Odds ratio comparing colstin/aminoglycoside based therapy to non-colistin/aminoglycoside based therapy from RIFLE criteria studies analysis in Chien 2020 (1.61) | 0.145 | 0.140 |
| OR\_AKI\_death\_halved | Odds ratio of mortality for AKI compared to no AKI derived from Kerr (2014) (5.11) | Odds ratio of mortality for AKI compared to no AKI halved (2.56) | 0.136 | 0.131 |
| double.ckd.risk | Risk of CKD as observed in Bucaloiu 2012 | Risk of CKD doubled to reflect potential higher propensity for CKD in HVCS | 0.151 | 0.148 |
| abs.increase | Odds ratios on mortality associated with nephrotoxicity from Bucaloiu 2012 are applied multiplicatively to underlying risk in HVCS | Absolute risk increases in Bucaloiu 2012 are assumed to apply | Change <10% relative to base case\* | 0.158 |
| all.aki.lt | Base case assumptions with respect to long-term effects of AKI | Applying a range of alternative assumptions to model the long-term effects of AKI | Change <10% relative to base case\* | 0.158 |
| loglogistic | Log-normal model fit to CARBAR survival data | loglogistic model fit to CARBAR survival data | 0.151\* | 0.148\* |
| weibull | Log-normal model fit to CARBAR survival data | Weibull model fit to CARBAR survival data | 0.120 | 0.116 |
| lt.care | No costs of long-term care | Costs of discharge to long-term care included  | Change <10% relative to base case\* | 0.197 |
| thresh15\* | Cost-effectiveness threshold £20,000 | Cost-effectiveness threshold £15,000 | 0.185 | 0.180 |
| thresh30\* | Cost-effectiveness threshold £20,000 | Cost-effectiveness threshold £30,000 | 0.164 | 0.159 |
| dr1.5\* | Discount rate for costs and benefits 3.5% | Discount rate for costs and benefits 1.5% | 0.197 | 0.193 |

AKI, acute kidney injury; CKD, chronic kidney disease; EUCAST, European Committee on Antimicrobial Susceptibility Testing; HVCS, high value clinical scenario; INHE, incremental net health effects; PHE, Public Health England

NB: Net health effects derived using threshold of £20,000/QALY.

\* Scenarios that modified the base case INHE by more than 10% in the report but not after correcting the model errors, or vice versa.

Updated figures and tables: population-level outcomes

Figure 5. Population-level INHE (QALYs) over 20 years based on two population size scenarios. (Update of Figure 20 in the EEPRU report)

P1: baseline population based on PHE categorisation of infection sites; P2: baseline population based on clinical advisors’ categorisation of infection sites; G1: damped growth rate; G2: growth rate not damped; R1: 1% resistance after 20 years; R2: 10% resistance after 20 years; R3: 30% resistance after 20 years

* 1. PHE categorisation



* 1. Expert-guided categorisation of specimen types



Table 11. Total population-level INHE across the first 20 years of usage. (Update of Table 42 in the EEPRU report)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Baseline population | Pop. growth rate | Change in resistance | HAP/ VAP (MBL *CPE*) | HAP/ VAP (PA MBL) | HAP/ VAP (Sten.) | cUTI (MBL *CPE*) | cUTI (PA MBL) | cUTI (Sten.) | BSI (MBL *CPE*) | BSI (PA MBL) | BSI (Sten.) | IAI (MBL *CPE*) | IAI (PA MBL) | IAI (Sten.) | Total |
| PHE categories of specimen types (scenario P1) | Model with damped effect G1) | 1% (R1) | 98 | 12 | 52 | 32 | 43 | 72 | 604 | 28 | 54 | 27 | 30 | 41 | 1,093 |
| 5% (R2) | 96 | 12 | 51 | 31 | 42 | 71 | 589 | 27 | 53 | 26 | 29 | 40 | 1,067 |
| 10% (R3) | 93 | 11 | 49 | 30 | 41 | 69 | 570 | 27 | 51 | 25 | 29 | 39 | 1,034 |
| 30% (R4) | 80 | 10 | 41 | 25 | 37 | 60 | 495 | 23 | 44 | 21 | 26 | 34 | 896 |
| Model without damped effect (G2) | 1% (R1) | 153 | 12 | 82 | 50 | 43 | 102 | 945 | 28 | 80 | 42 | 30 | 58 | 1,625 |
| 5% (R2) | 149 | 12 | 79 | 49 | 42 | 99 | 918 | 27 | 78 | 40 | 29 | 57 | 1,579 |
| 10% (R3) | 144 | 11 | 75 | 46 | 41 | 96 | 884 | 27 | 75 | 39 | 29 | 55 | 1,522 |
| 30% (R4) | 122 | 10 | 61 | 38 | 37 | 83 | 749 | 23 | 64 | 31 | 26 | 47 | 1,291 |
| Clinical advisors’ categories of specimen types (scenario P2) | Model with damped effect G1) | 1% (R1) | 613 | 185 | 794 | 44 | 26 | 53 | 604 | 28 | 54 | 27 | 30 | 41 | 2,499 |
| 5% (R2) | 598 | 180 | 777 | 42 | 25 | 52 | 589 | 27 | 53 | 26 | 29 | 40 | 2,438 |
| 10% (R3) | 579 | 174 | 755 | 41 | 25 | 50 | 570 | 27 | 51 | 25 | 29 | 39 | 2,365 |
| 30% (R4) | 502 | 151 | 669 | 34 | 22 | 43 | 495 | 23 | 44 | 21 | 26 | 34 | 2,064 |
| Model without damped effect (G2) | 1% (R1) | 959 | 185 | 1,059 | 68 | 26 | 79 | 945 | 28 | 80 | 42 | 30 | 58 | 3,559 |
| 5% (R2) | 932 | 180 | 1,033 | 66 | 25 | 77 | 918 | 27 | 78 | 40 | 29 | 57 | 3,462 |
| 10% (R3) | 897 | 174 | 1,001 | 63 | 25 | 74 | 884 | 27 | 75 | 39 | 29 | 55 | 3,343 |
| 30% (R4) | 760 | 151 | 874 | 51 | 22 | 63 | 749 | 23 | 64 | 31 | 26 | 47 | 2,861 |

BSI, bloodstream infection; CPE, carbapenem-producing *Enterobacterales*; cUTI, complicated urinary tract infection; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia; IAI, intra-abdominal infection; MBL, metallo-beta-lactamases; PHE, Public Health England; PA, Pseudomonas; Steno, Stenotrophomonas

Figure 6. Distribution of total population INHEs of cefiderocol (2,000 simulations). (Update of Figure 21 in the EEPRU report)



Abbreviations: CrI, 95% credible interval.

P1G1: baseline population (point estimate) based on PHE categorisation of infection sites, growth rate damped (uncertain); P2G2: baseline population (point estimate) based on clinical advisors’ categorisation of infection sites, growth rate not damped (uncertain).

Table 12: Population-level INHE (QALYs) for patient-level scenario analyses (deterministic) – range derived from different assumptions about the population size (scenarios P1G1 and P2G2 in Figure 15). (Update of Table 43 in EEPRU report)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Base case value/assumption** | **Scenario value/assumption** | **HAP/VAP *Enterobacterales* (ES)** | **HAP/VAP** PA **(ES)** | **HAP/VAP Sten. (MDS)** | **cUTI *Enterobacterales* (MDS)** | **cUTI** PA **(MDS)** | **cUTI Sten. (MDS)** | **BSI *Enterobacterales* (ES)** | **BSI** PA **(ES)**  | **BSI Sten. (MDS)** | **IAI *Enterobacterales* (MDS)** | **IAI**PA **(MDS)** | **IAI Sten. (MDS)** | **Total** |
| Base-case | 99-966 | 12-186 | 53-1,065 | 32-69 | 26-43 | 73-79 | 608-952 | 28-28 | 54-81 | 27-42 | 30-30 | 41-59 | 1,100-3,583 |
| Probability patient has MBL *Enterobacterales* is 0.15, MBL Pseudo. is 0.14 | Probability patient has MBL is 0.71 based on BSAC survey data | 01-12 | 17-269 | 53-1,065 | 32-69 | 26-43 | 73-79 | 8-12 | 41-41 | 54-81 | 27-42 | 30-30 | 41-59 | 420-1,785 |
| Probability patient has MBL *Enterobacterales* is 0.15, MBL Pseudo. is 0.14 | Probability patient has MBL is 0.30 | 65-637 | 18-282 | 53-1,065 | 32-69 | 26-43 | 73-79 | 401-628 | 43-43 | 54-81 | 27-42 | 30-30 | 41-59 | 880-3,041 |
| Probability patient has MBL *Enterobacterales* is 0.15, MBL Pseudo. is 0.14 | Probability patient has MBL is 0.40 | 42-413 | 18-279 | 53-1,065 | 32-69 | 26-43 | 73-79 | 260-407 | 43-43 | 54-81 | 27-42 | 30-30 | 41-59 | 716-2,593 |
| Probability patient has MBL *Enterobacterales* is 0.15, MBL Pseudo. is 0.14 | Probability patient has MBL is 0.50 | 19-189 | 18-276 | 53-1,065 | 32-69 | 26-43 | 73-79 | 119-187 | 42-42 | 54-81 | 27-42 | 30-30 | 41-59 | 551-2,145 |
| Probability patient has MBL *Enterobacterales* is 0.15, MBL Pseudo. is 0.14 | Probability patient has MBL is 0.60 | 01-10 | 17-273 | 53-1,065 | 32-69 | 26-43 | 73-79 | 06-10 | 42-42 | 54-81 | 27-42 | 30-30 | 41-59 | 419-1,786 |
| Probability patient has MBL *Enterobacterales* is 0.15, MBL Pseudo. is 0.14 | Probability patient has MBL is 0.70 | 01-12 | 17-269 | 53-1,065 | 32-69 | 26-43 | 73-79 | 08-12 | 41-41 | 54-81 | 27-42 | 30-30 | 41-59 | 420-1,785 |
| Probability patient has MBL *Enterobacterales* is 0.15, MBL Pseudo. is 0.14 | Probability patient has MBL is 0.80 | 1-14 | 17-266 | 53-1,065 | 32-69 | 26-43 | 73-79 | 9-14 | 41-41 | 54-81 | 27-42 | 30-30 | 41-59 | 421-1,786 |
| Probability patient has MBL *Enterobacterales* is 0.15, MBL Pseudo. is 0.14 | Probability patient has MBL is 0.90 | 2-15 | 17-263 | 53-1,065 | 32-69 | 26-43 | 73-79 | 10-15 | 40-40 | 54-81 | 27-42 | 30-30 | 41-59 | 422-1,784 |
| Susceptibility (*Enterobacterales* and PsA) based on NMA of EUCAST studies | Susceptibility based on NMA of CLSI studies | 122-1,194 | 02-34 | 25-275 | 16-33 | 5-9 | 21-28 | 751-1,177 | 5-5 | 19-28 | 13-20 | 6-6 | 12-18 | 1,001-2,823 |
| Susceptibility (*Enterobacterales* and PsA) based on NMA of EUCAST studies | Susceptibility based on PHE data, with cefiderocol and fosfomycin data from separate cefiderocol and fosfomycin networks (CLSI studies). | 134-1,316 | 1-9 | 40-213 | 25-53 | 1-2 | 21-34 | 828-1,297 | 1-1 | 23-34 | 21-32 | 2-2 | 13-18 | 1,111-3,010 |
| Susceptibility (*Enterobacterales* and PsA) based on NMA of EUCAST studies | MBL *Enterobacterales* susceptibility based on PHE data (cefiderocol from NMA) | 95-934 | 12-186 | 130-1,389 | 80-171 | 26-43 | 108-141 | 588-921 | 28-28 | 96-142 | 67-105 | 30-30 | 63-90 | 1,340-4,163 |
| Susceptibility (*Enterobacterales* and PsA) based on NMA of EUCAST studies | PsA MBL susceptibility based on NMA of EUCAST studies, absolute colistin susceptibility values from SIDERO WT | 99-966 | 12-180 | 53-1,448 | 32-69 | 38-64 | 97-99 | 608-952 | 27-27 | 67-99 | 27-42 | 45-45 | 54-77 | 1,185-4,042 |
| Probability of AKI with colistin/aminoglycoside therapy based on Sisay 2021 (0.45) | Probability of AKI with colistin/aminoglycoside therapy based on Chien (0.32) | 75-732 | 11-171 | 47-891 | 29-62 | 76-46 | 105-109 | 460-721 | 26-26 | 47-69 | 24-38 | 54-54 | 60-86 | 1,018-3,001 |
| Odds ratio comparing AKI for colistin/ aminoglycoside-based therapy to non-colistin/aminoglycoside-based therapy from all studies analysis in Chien 2020 (1.81) | Odds ratio from all studies analysis in Wagenlehner 2021 (2.23) | 137-1,341 | 12-185 | 62-1,344 | 38-82 | 66-110 | 147-155 | 844-1,322 | 28-28 | 67-100 | 32-50 | 77-77 | 85-122 | 1,647-4,864 |
| Odds ratio comparing AKI for colistin/ aminoglycoside-based therapy to non-colistin/aminoglycoside-based therapy from all studies analysis in Chien 2020 (1.81) | Odds ratio from RIFLE criteria studies analysis in Chien 2020 (1.61) | 75-732 | 12-188 | 47-896 | 29-61 | 26-43 | 70-75 | 460-721 | 29-29 | 47-69 | 24-38 | 30-30 | 39-56 | 905-2,921 |
| CARBAR unadjusted baseline mortality | CARBAR adjusted to remove impact of AKIs | Change <10% relative to base case\* |
| Risk of CKD as observed in Bucaloiu 2012 | Risk of CKD doubled to reflect potential higher propensity for CKD in HVCS | 80-782 | 11-174 | 46-925 | 28-61 | 37-22 | 64-70 | 492-770 | 27-27 | 48-70 | 24-37 | 26-26 | 36-51 | 919-3,015 |
| Odds ratios on mortality associated with nephrotoxicity from Bucaloiu 2012 are applied multiplicatively to underlying risk in HVCS | Absolute risk increases in Bucaloiu 2012 are assumed to apply | Change <10% relative to base case\* |
| Base case assumptions with respect to long-term effects of AKI | Applying a range of alternative assumptions to model the long-term effects of AKI | Change <10% relative to base case\* |
| No costs of long-term care | Costs of discharge to long-term care  | Change <10% relative to base case\* |
| Log-normal model fit to CARBAR survival data | Loglogistic model fit to CARBAR survival data | 80-783 | 11-174 | 46-925 | 28-61 | 21-35 | 61-68 | 492-771 | 27-27 | 48-70 | 24-37 | 25-25 | 35-50 | 912-3,012 |
| Log-normal model fit to CARBAR survival data | Weibull model fit to CARBAR survival data | 56-545 | 10-158 | 38-739 | 23-49 | 55-33 | 79-80 | 343-537 | 24-24 | 38-57 | 19-30 | 38-38 | 44-63 | 768-2,352 |
| Odds ratio of mortality for AKI compared to no AKI derived from Kerr (2014) (5.11) | Odds ratio of mortality for AKI compared to no AKI halved (2.56) | 73-710 | 11-179 | 45-850 | 28-59 | 45-27 | 72-76 | 447-699 | 27-27 | 45-66 | 23-36 | 32-32 | 41-58 | 889-2,819 |

BSI, bloodstream infection; CPE, carbapenem-producing *Enterobacterales*; cUTI, complicated urinary tract infection; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia; IAI, intra-abdominal infection; MBL, metallo-beta-lactamases; PHE, Public Health England; PA, *Pseudomonas aeruginosa*; RIFLE, risk, injury, failure, loss and end-stage renal disease; Steno, Stenotrophomonas

\* Scenarios that modified the base case INHE by more than 10% in the report but not after correcting the model errors, or vice versa.

Table 13. Total INHE across 10 years of usage. (Update of Table A20.1 in Appendix 20 of the EEPRU report)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Baseline population | Pop. growth rate | Change in resistance | HAP/ VAP (CPE MBL) | HAP/ VAP (Pseud. MBL) | HAP/ VAP (Sten.) | cUTI (CPE MBL) | cUTI (Pseud. MBL) | cUTI (Sten.) | BSI (CPE MBL) | BSI (Pseud. MBL) | BSI (Sten.) | IAI (CPE MBL) | IAI (Pseud. MBL) | IAI (Sten.) | Total | Proportion of 20 year INHE (%) |
| PHE categories of specimen types (scenario P1) | Model with damped effect G1) | 1% (R1) | 49 | 7 | 26 | 16 | 25 | 37 | 301 | 17 | 28 | 13 | 17 | 21 | 557 | 51 |
| 5% (R2) | 48 | 7 | 26 | 16 | 25 | 37 | 298 | 16 | 27 | 13 | 17 | 21 | 551 | 52 |
| 10% (R3) | 48 | 7 | 25 | 15 | 24 | 36 | 293 | 16 | 27 | 13 | 17 | 20 | 541 | 52 |
| 30% (R4) | 45 | 6 | 23 | 14 | 23 | 34 | 275 | 15 | 25 | 12 | 16 | 19 | 507 | 57 |
| Model without damped effect (G2) | 1% (R1) | 60 | 7 | 32 | 20 | 25 | 44 | 370 | 17 | 33 | 16 | 17 | 25 | 666 | 41 |
| 5% (R2) | 59 | 7 | 31 | 19 | 25 | 43 | 366 | 16 | 33 | 16 | 17 | 25 | 657 | 42 |
| 10% (R3) | 58 | 7 | 31 | 19 | 24 | 43 | 359 | 16 | 32 | 16 | 17 | 24 | 646 | 42 |
| 30% (R4) | 54 | 6 | 28 | 17 | 23 | 40 | 335 | 15 | 30 | 15 | 16 | 23 | 602 | 47 |
| Clinical advisors’ categories of specimen types (scenario P2) | Model with damped effect G1) | 1% (R1) | 306 | 108 | 419 | 22 | 15 | 27 | 301 | 17 | 28 | 13 | 17 | 21 | 1,294 | 52 |
| 5% (R2) | 302 | 107 | 414 | 21 | 15 | 27 | 298 | 16 | 27 | 13 | 17 | 21 | 1,278 | 52 |
| 10% (R3) | 297 | 105 | 408 | 21 | 15 | 26 | 293 | 16 | 27 | 13 | 17 | 20 | 1,258 | 53 |
| 30% (R4) | 279 | 98 | 386 | 19 | 14 | 25 | 275 | 15 | 25 | 12 | 16 | 19 | 1,183 | 57 |
| Model without damped effect (G2) | 1% (R1) | 376 | 108 | 479 | 27 | 15 | 32 | 370 | 17 | 33 | 16 | 17 | 25 | 1,515 | 43 |
| 5% (R2) | 371 | 107 | 474 | 26 | 15 | 32 | 366 | 16 | 33 | 16 | 17 | 25 | 1,498 | 43 |
| 10% (R3) | 365 | 105 | 467 | 26 | 15 | 32 | 359 | 16 | 32 | 16 | 17 | 24 | 1,474 | 44 |
| 30% (R4) | 340 | 98 | 440 | 24 | 14 | 29 | 335 | 15 | 30 | 15 | 16 | 23 | 1,379 | 48 |

BSI, bloodstream infection; CPE, carbapenem-producing *Enterobacterales*; cUTI, complicated urinary tract infection; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia; IAI, intraabdominal infection; MBL, metallo-beta-lactamases; PHE, Public Health England; Pseud, Pseudomonas; Steno, Stenotrophomonas