



**Final report for the technology evaluation of ceftazidime with avibactam: addendum relating to scenario analyses**

**20th January 2022**

# Scenario 1: Future population health gains scenario

## Background

Based on advice from clinical advisors, EEPRU has modelled a level of expected usage for the new antimicrobials (CAZ-AVI and cefiderocol) that reflects a relatively restrictive stewardship policy. An important expected benefit of such a policy is that future cohorts of patients can benefit from the new drugs as they will continue to be effective in the long term. These longer-term population health gains resulting from restricted short-term use have been described in the literature as ‘insurance value’. Feedback from NICE, the committee and consultees to the NICE process has questioned the extent to which the EEPRU evaluation work fully captures this aspect of benefit from the new products.

The EEPRU evaluation work has captured these long-term benefits to the extent that they accrue to patients within the quantified areas of expected usage, and assuming that, within these highly resistant infections, the level of resistance to existing drugs is constant over time. The latter assumption was based on available time series data on drug susceptibility.

There are several reasons why this may not fully quantify longer-term benefits:

1. We may see higher levels of resistance to existing drugs within the areas of expected usage over time.
2. We may see multi-drug resistant pathogens, against which the new drugs are effective, emerge that are currently rare or even unknown.
3. We may see pathogens that are currently treatable with existing therapies (and are not therefore included in the areas of expected usage) become resistant.

If one or more of these factors emerge, they would be expected to occur in the long-term and quite possibly beyond 20 years.

Conducting quantitative modelling of these effects is unavoidably highly speculative; however, the committee may wish to reflect on these possibilities. Therefore, EEPRU has developed an additional scenario for exploring the magnitude of these effects.

## Methods

The scenario aimed to explore the effect on incremental net health effects (INHEs) of CAZ-AVI in case of emergence of multi-resistant pathogens against which CAZ-AVI is the only effective treatment and, in that product’s absence, clinicians would be forced to use multidrug salvage therapy.

### Patient-level benefit

The patient-level benefit was derived by adapting the model in the EEPRU report. Specifically, we assumed that, in patients with these new highly resistant infections, existing therapies are no longer effective. In this model, this was achieved by setting the susceptibility for all comparators to zero. Under this illustrative scenario, no safety differences are assumed as it is expected that, if treatments become completely ineffective, no treatment or only safe antimicrobials will be used. Furthermore, the susceptibility for CAZ-AVI is set to 90% (an estimate broadly reflecting the susceptibility across different scenarios in the report), and maintained at this level over the long-term, although we note that this is likely to overestimate INHEs as susceptibility to CAZ-AVI may be expected to wane over time.

In the ES, we assume everyone gets CAZ-AVI or non-colistin/aminoglycosides (comparator), then 5 days later they move into the MDS, and switch to the treatment they are susceptible to. For both CAZ-AVI and the comparator, 80% of the patients are assumed not have the target MDR infection (as in the base-case modelling) and these patients receive something else. When CAZ-AVI is available, the 20% who do have that target infection receive either CAZ-AVI (for 90% who are susceptible) or salvage therapy (for the 10% not susceptible to CAZ-AVI). When CAZ-AVI is not available, 100% of patients receive salvage therapy (the comparator).

In MDS we assume 90% CAZ-AVI/10% salvage therapy (when CAZ-AVI is available) or 100% salvage therapy (comparator).

The results represent the lifetime patient-level INHE of CAZ-AVI relative to multidrug salvage therapy expressed in QALYs.

### Population-level benefit

To derive population-level benefits, patient level INHE is multiplied by the expected population size over the relevant time horizon and the probability of this scenario occurring. The patient-level INHE was assumed to remain constant over time. The population size is increased over time at a constant rate relative to baseline. Population benefits over time were discounted to reflect the delay in benefits received. Note that the relevant population here is not the same as the expected population in the main EEPRU report as these assumed to be entirely different pathogens.

The hypothetical nature of the scenario meant that there was no formal evidence to inform the extrapolation parameters and, as result, the parameter ranges were provided by the Committee. However, given the highly speculative nature of the analysis, EEPRU provided a flexible Excel-based tool, with user defined parameters, to support Committee deliberations in assessing the potential additional long-term health effects that may result from CAZ-AVI usage.

Table . Extrapolation parameters used in the base-case of the scenario and sensitivity analysis

|  |  |
| --- | --- |
| User defined parameter | Base-case (range) |
| Probability of event (emergence of highly resistant strains) | 1% (0.5% - 5%) |
| Time of first event (from now) | 10 years (5 – 15 years) |
| The number of patients affected in the first year | 25 individuals (25-100) |
| The annual growth in the number of infections (from baseline) | 20% (3% - 30%) |
| Analysis time horizon (years) | 50 (20-50) |
| Population discount rate | 3.5% |

The modifiable parameters in the Excel tool include the six extrapolation parameters: the probability of emergence of the highly resistant strains; the time of the first event; the number of patients affected in the first year; the annual growth rate in the number of infections (constant, relative to baseline); the analysis time horizon; and the discount rate.

In addition, the user can specify the site of infection and treatment setting reflected in the results (HAP/VAP empiric setting, HAP/VAP microbiology-directed setting and cUTI microbiology directed setting), or an alternative patient-level INHE reflecting the impact of these highly resistant infections in an alternative population.

The parameter estimates to use in the model were sought from the Committee and have been based on David Partridge’s email to NICE dated 30th December 2021 (Table 1).

## Results

The patient-level INHEs in the base-case from the main EEPRU report and as used in this additional scenario, expressed in QALYs per patient, are shown in Table 2. In summary, assuming all specific existing treatment options have zero effectiveness increases the patient-level INHE for all sites and settings. The increase is greatest in the microbiology-directed setting, as all patients benefit from the treatment with CAZ-AVI, compared to the empiric setting where only 20% of people have the suspected pathogen-mechanism (as per EEPRU report, Table 26).

Table 2. Patient-level INHE (QALYs/patient)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **HAP/VAP, ES** | **HAP/VAP, MDS** | **cUTIs, MDS** |
| **Base-case** | 0.163 compared to nca0.215 compared to ca | 0.071 | 0.069 |
| **New scenario** | 0.395 | 1.031 | 1.032 |

cUTI, complicated urinary tract infection; ca, colistin/aminoglycosides; ES, empiric setting; HAP/VAP, hospital acquired pneumonia/ventilator associated pneumonia; MDS, microbiology-directed setting; nca, non-colistin/aminoglycosides.

The population-level INHE (assuming patient-level benefit in cUTIs - the site with the highest patient-level INHE) is shown in Table 3 for a range of population-related scenarios. Overall, the benefit is relatively low (between 0.8 and 58.4 QALYs) compared to the benefit in EEPRU HVCSs (between 629 and 2,211 QALYs).

Table 3. Population-level results using the scenario base-case assumptions and sensitivity analyses

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Value/assumption in base-case** | **Value/assumption in sensitivity analyses** | **Total number of patients** | **Total INHE (QALYs) conditional on event occurring** | **Expected INHE (QALYs)** |
| Base-case, parameter values shown in Table 1 | 4,720 | 1460 | 14.6 |
| Probability of event = 1% | Probability of event = 0.5% | 4,720 | 1460 | 7.3 |
| Probability of event = 1% | Probability of event = 5% | 4,720 | 1460 | 73.0 |
| Event occurs in 10 years | Event occurs in 5 years | 6,195 | 2180 | 21.8 |
| Event occurs in 10 years | Event occurs in 15 years | 3,245 | 870 | 8.7 |
| Number of patients in year 1 = 25 | Number of patients in year 1 = 100 | 18,880 | 5839 | 58.4 |
| Population growth = 20% | Population growth = 3% | 1,388 | 452 | 4.5 |
| Population growth = 20% | Population growth = 30% | 6,680 | 2053 | 20.5 |
| Analysis time horizon = 50 years | Analysis time horizon = 20 years | 145 | 79 | 0.8 |

INHE, incremental net health effects; QALYs, quality adjusted life years.

**Scenario 2: Accounting for the benefit in patients who cannot take colistin/aminoglycosides**

**Background**

The analysis in the EEPRU report was based on a proportion of patients being resistant to existing therapies other than colistin/aminoglycosides. In which case it was assumed that, in the absence of CAZ-AVI, colistin/aminoglycosides would be administered to patients. The negative health effects and additional costs of renal toxicity associated with these products were explicitly modelled in assessing the patient-level INHEs of CAZ-AVI compared with existing therapies. Based the results of the network meta-analysis of EUCAST studies (Section 7.2.3.2 of the EEPRU report), 65% of patients shown to have OXA-48 in the ES were resistant to existing therapies other than colistin/aminoglycosides. In the MDS, 35% of patients were resistant to existing therapies other than colistin/aminoglycosides.

Consultees have indicated that, in terms of existing therapies (i.e., in world without CAZ-AVI), there is a proportion of patients who would not receive colistin/aminoglycosides even if no other effective therapy was available. This would be due to a patient’s high clinical risk of renal toxicity. For such patients it can be assumed that they would only receive salvage therapy. The size of this sub-group of patients contraindicated to colistin/aminoglycosides was considered small by EEPRU’s clinical advisors. The Committee has requested a scenario which considers the magnitude of population-level INHEs for this sub-group using the Committee’s assumptions about the size of the cohort as a proportion of those estimated for the HVCSs in the report.

**Methods**

The scenario aimed to reflect the benefit of CAZ-AVI in patients who cannot take colistin and other aminoglycoside treatments and, therefore, without the new drug, would receive multidrug salvage therapy.

### Patient-level benefit

For this scenario, the patient-level INHEs in those who can take colistin (the EEPRU base-case) and those who cannot are shown in Table 4. In the empiric setting (HAP/VAP and BSIs), the incremental patient-level benefit of CAZ-AVI was derived by combining the EEPRU base-case and Scenario 1 above. In patients who were treated empirically and who were later confirmed to have an infection caused by OXA-48 (20% of patients, Table 26 of the EEPRU report), outcomes were derived from Scenario 1 above, assuming that, without CAZ-AVI, all patients received ineffective empiric treatment. The incremental benefit of CAZ-AVI in this sub-group was 2.2 QALYs per person. In patients who were treated empirically and who were later confirmed not to have an infection caused by OXA-48 (80% of the sample), outcomes with colistin and with salvage therapy were assumed to be the same (0.221 QALYs in the amended Table 36 of the EEPRU report).

In the MDS (cUTI and IAI, as discussed in Section 7.5.2.7 of the EEPRU report), without CAZ-AVI, patients who cannot take colistin/aminoglycosides were assumed to receive multidrug salvage therapy. The incremental benefit of CAZ-AVI was derived in Scenario 1 above (1.032 for cUTIs in Table 2).

**Table 4. Patient-level INHE (QALYs/patient)**

|  |  |  |
| --- | --- | --- |
|  | **ES1** | **MDS2** |
| **Base-case** | 0.215 | 0.069 |
| **New scenario** | 0.622 | 1.032 |

Abbreviations: ES, empiric setting; MDS, microbiology-directed setting.

1 Derived from the HAP/VAP model but applied to HAP/VAP and BSI

2 Derived from the cUTI model but applied to cUTI and IaI

### Population-level benefit

The scenario was implemented by updating the Excel tool derived for Scenario 1 above, to reflect the updated patient-level INHE (Table 4) and the extrapolation parameters shown in Table 5.

The initial population size was site and setting specific, derived as described in the Section 7.5.2.7 of the EEPRU report. Two different scenarios for the initial population size were explored derived from different classifications of specimen samples in SGSS dataset (Scenarios P1 and P2 in Table 34 or the EEPRU report). The population growth rate was assumed to be the same across all sites of infection and settings. It was approximated using the population size in year 1 and year 20 in the report (shown in Figure 21), assuming a constant rate of increase between those two time points. Two scenarios for the population growth rate were explored derived assuming damped and non-damped population growth trends (Scenarios G1 and G2 in Figure 21 in the EEPRU report) – these correspond to 1.2% and 17.1% annual increase on baseline in the Excel tool.

Table . Extrapolation parameters

|  |  |
| --- | --- |
| User defined parameter | Base-case (range) |
| Probability of event (emergence of highly resistant strains) | 100% |
| Time of event (from now) | 0 years |
| The number of patients affected in the first year | See Table 34 of the EEPRU report |
| The annual growth in the number of infections (from baseline) | 1.2% or 17.1% |
| Analysis time horizon (years) | 20 |
| Population annual discount rate | 3.5% |

The overall benefit was derived by averaging the total INHE from the base-case and the new scenario, weighted by the proportion of the total treated population who are susceptible to colistin/aminoglycosides but would be given salvage therapy due to colistin/aminoglycoside toxicity.

Considering the lack of empiric evidence, the NICE Committee suggested a plausible range (20% – 40%) for the proportion of patients who, despite being susceptible to colistin/aminoglycosides, would instead be given salvage therapy due to colistin/aminoglycoside toxicity, in the absence of CAZ-AVI.

In the empiric setting (HAP/VAP and BSIs), this represents 20% - 40% of the total treated population when colistin/aminoglycosides are used empirically.

In the microbiology-directed setting (cUTI and IAI), the scenario is assumed to be applicable to 20% - 40% of the patients who were not susceptible to non-colistin/aminoglycoside therapy (100% - 65% = 35% of the sample, as per Table 24 of the EEPRU report), assuming that all such patients would be considered for colistin/aminoglycoside therapy. Therefore, the proportion of the total sample in the MDS who would be in this sub-group was between 7% (= 0.2\*35%) and 14% (= 0.4\*35%).

**Results**

Figure 1 shows how the total expected INHE changes with the proportion of patients who cannot take colistin, compared to the EEPRU base-case. In summary, reflecting the outcomes of patients who cannot take colistin/aminoglycosides increases the benefit of CAZ-AVI, and the benefit increases with the proportion of such patients. The absolute increase in INHE in this scenario increases with the population size, as shown by the orange solid and dashed lines (representing a scenario with a higher patient population) diverging more than the blue solid and dashed lines.

Figure . Change in total population-level INHE with varying proportion of patients who cannot take colistin, derived from different assumptions about the population size.

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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.

Table 6 shows the breakdown of the population-level INHE for each site of infection for a range of proportions of patients who cannot take colistin/aminoglycosides, compared to the EEPRU base-case. The change in INHE compared to the base-case is higher in the MDS (cUTI and IAI) than the ES (HAP/VAP and BSI) because the patient-level benefit of CAZ-AVI in patients who cannot take colistin is higher in the MDS than the ES (shown in Table 2).

Table . Total population-level INHE (QALYs) per site of infection

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Proportion of susceptible patients who cannot take ca | HAP/VAP1 | cUTI1 | BSI1 | IAI1 | Total1 |
| 0% (base-case)2 | 66 - 946 | 83 - 274 | 444 - 916 | 36 - 75 | 629 - 2,211 |
| 20% | 102 – 1,546 | 174 - 619 | 683 – 1,499 | 76 - 169 | 1,035 – 3,833 |
| 40% | 137 – 2,147 | 265 - 965 | 922 – 2,081 | 116 - 263 | 1,441 – 5,456 |

Abbreviations: cUTI, complicated urinary tract infection; ca, colistin/aminoglycosides; HAP/VAP, hospital acquired pneumonia/ventilator associated pneumonia; INHE, incremental net health effects; 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.

1 Ranges represent mean INHE (QALYs) for the two most extreme scenarios regarding the population size and growth, P1G1 and P2G2 in the EEPRU report.

2 In the base-case resistance to CAZ-AVI was assumed to increase by 1% over 20 years. This assumption was not applied in the new scenarios.

These expected population-level INHE may overestimate the total INHE for several reasons. Firstly, the 20%-40% proportion of patients who would not be given colistin/aminoglycosides because of toxicity fears in the absence of CAZ-AVI is high compared to the assessment of the clinical advisors consulted by EEPRU. Secondly, the scenario assumes that outcomes in patients who can and cannot take colistin/aminoglycosides are comparable when, in practice, patients who cannot take colistin may have poorer prognoses than patients who can. Thirdly, the scenario assumes patients would be contraindicated to colistin *and* aminoglycosides, but clinical advisors to EEPRU (and consultation comments from the British Infection Association) suggested that most of the concern is about colistin.

Finally, the scenario results in Table 6 represent the benefit in HVCSs when, in the ES, all patients with suspected OXA-48 infection are treated with colistin/aminoglycosides. In the EEPRU base-case, the empiric treatment with non-colistin/glycoside therapy had a higher patient-level net benefit (and lower incremental benefit of CAZ-AVI) than treatment with colistin/glycosides, suggesting that, without CAZ-AVI, non-aminoglycosides are the preferred empiric treatment. The base-case results in the EEPRU report and in Table 6 reflect this lower incremental benefit of CAZ-AVI achieved when only non-colistin/aminoglycosides are used as first line empiric treatment.

The benefit of CAZ-AVI generated in patients who are susceptible to, but who cannot take colistin, in the ES is likely to be lower than the estimates in Table 6 if empiric treatment does not include colistin/aminoglycosides. This is because it would only apply to between 6% and 12% of the total sample of patients in this setting (20% to 40% of the 13% (0.2 x 65%) who have the infection but are not susceptible to the empiric treatment with non-aminoglycosides). The benefit in this subpopulation could not be quantified as EEPRU did not explicitly model the second line of treatment in the ES. The lower bound of the estimate, assuming no added benefit of CAZ-AVI when suspected OXA-48 infections are treated with non-colistin/aminoglycosides in the ES, leads to 760-2,651 QALYs if 20% of susceptible patients cannot take colistin/aminoglycosides, and 891 – 3,090 QALYs if that proportion is 40%.