**Data relating to susceptibility for cefiderocol and comparators**

We thank you for your response to our data request. After consideration of the new data, we have identified some additional data that would help our synthesis. However, these would need to be provided to us extremely quickly in order for us to be able to include them in our analysis. We appreciate this may not be possible. The rationale for needing the data and the data required is described below. We would need data by Monday 16th August. If it is not possible to fulfil the entire data request, the priority would be for data that would allow us to include **SIDERO-WT** and **Dobias et al. 2017** in our review, as detailed below

**Rationale**

       Data for SIDERO-WT from Kazmierczak et al 2019 does not report the susceptibility of cefiderocol for MBLs, and the data request response used a different data cut, which we think included more years of data, and possibly applied different inclusion criteria relating to carbapenem sensitivity. We currently cannot include SIDERO-WT in our synthesis since we do not have data for cefiderocol and comparators from the same data cut. To include SIDERO-WT, we would either need:

* the susceptibility of MBLs to cefiderocol, using the same data cut as Kazmierczak et al. 2019 (to complete the data reported for comparators in Kazmierczak et al)
* or the comparator data using the same data cut as the response to our data request (see “Data required” below).

       Data from SIDERO-CR from Longshaw et al 2020 covers only Europe, whereas the data request shows that there is additional worldwide data. After consultation with our clinical advisers, ideally we would include all data in the synthesis.

* Data from Johnston et al. 2020 and Dobias et al. 2017 also appears to fit out inclusion criteria, however the way the data are presented in the published reports prevents us from using them. Neither report EUCAST breakpoints, whilst Dobias et al does not report the percentage of isolates susceptible (only the range and MIC 50 and 90). If possible we would like both sets of data giving percent of isolates susceptible to cefiderocol and comparators using the breakpoint cut-offs as detailed in “Data required” below.

**Data required**

We are interested in data showing the percent of isolates that are susceptible to cefiderocol and any data for our comparators of interest from SIDERO-CR (worldwide if available, all available years), SIDERO-WT (worldwide if available, all available years), and the cohorts reported in Johnston et al. 2020; and Dobias et al. (if this is available to you) for MBLs:

- Reporting CPE and PA separately

- Restricted to carriage or co-carriage of MBLs

- Report data using the EUCAST cut off for cefiderocol (2mg/L) and EUCAST cut-offs for comparators - NB the response to the data request lists breakpoints used, but these do not appear to match EUCAST breakpoints e.g. meropenem’s breakpoint for CPE has been 2mg/L since at least 2010, not 16 as reported in the data request; for colistin it has been 2mg/L since at least 2010 for CPE, not 4mg/L as stated in the response to the data request.

- Report data separately using the CLSI cut off for cefiderocol (4mg/L) and CLSI cut-offs for comparators

- not restricted by carbapenem sensitivity, or any other sensitivity or phenotype (where possible. Where criteria were used to select isolates, please detail what these were)

- counting intermediate susceptibility as resistant.

An example data table is provided below; please provide separate data tables for EUCAST and CLSI cut offs

**Table 1 EUCAST:**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Cefiderocol n/N (%) | Colistin  n/N (%) | Meropenem  n/N (%) | Tigecycline  n/N (%) | Aztreonam  n/N (%) | Fosfomycin  n/N (%) | Gentamicin  n/N (%) | Amikacin  n/N (%) | Tobramycin  n/N (%) |
| Breakpoints applied | EUCAST | EUCAST | EUCAST | EUCAST | EUCAST | EUCAST | EUCAST | EUCAST | EUCAST |
| SIDERO-WT |  |  |  |  |  |  |  |  |  |
| CPE MBL | 86/131 (65.6%) | 106/131 (80.9%) | 5/131 (3.8% | Null\* |  |  |  |  |  |
| PA MBL | 161/166 (96.9%) | 163/166 (98.1%) | 0/166 (0%) | Null\* |  |  |  |  |  |
| SIDERO-CR |  |  |  |  |  |  |  |  |  |
| CPE MBL | 123/190 (64.7%) | 167/190 (87.9%) | 6/190 (3.2%) | Null\* |  |  |  |  |  |
| PA MBL | 114/115 (99.1%) | 115/115 (100% | 1/115 (0.87%) | Null\* |  |  |  |  |  |
| Johnston et al. (2020) |  |  |  |  |  |  |  |  |  |
| CPE MBL |  |  |  |  |  |  |  |  |  |
| PA MBL |  |  |  |  |  |  |  |  |  |
| Dobias et al. (2017) |  |  |  |  |  |  |  |  |  |
| CPE MBL |  |  |  |  |  |  |  |  |  |
| PA MBL |  |  |  |  |  |  |  |  |  |

**Table 2 CSLI:**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Cefiderocol n/N (%) | Colistin  n/N (%) | Meropenem  n/N (%) | Tigecycline  n/N (%) | Aztreonam  n/N (%) | Fosfomycin  n/N (%) | Gentamicin  n/N (%) | Amikacin  n/N (%) | Tobramycin  n/N (%) |
| Breakpoints applied | CLSI | CLSI | CLSI | CLSI | CLSI | CLSI | CLSI | CLSI | CLSI |
| SIDERO-WT |  |  |  |  |  |  |  |  |  |
| CPE MBL | 128/131 (97.7%) | 103/131 (78.6%) | 1/131 (0.7%) | Null\* |  |  |  |  |  |
| PA MBL | 166/166 (100%) | 134/166 (80.7%) | 0/166 (0%) | Null\* |  |  |  |  |  |
| SIDERO-CR |  |  |  |  |  |  |  |  |  |
| CPE MBL | 173/190 (91.1%) | 162/190 (85.3%) | 0/190 (0%) | Null\* |  |  |  |  |  |
| PA MBL | 115/115 (100%) | 109/115 (94.8%) | 0/115 (0%) | Null\* |  |  |  |  |  |
| Johnston et al. (2020) |  |  |  |  |  |  |  |  |  |
| CPE MBL |  |  |  |  |  |  |  |  |  |
| PA MBL |  |  |  |  |  |  |  |  |  |
| Dobias et al. (2017) |  |  |  |  |  |  |  |  |  |
| CPE MBL |  |  |  |  |  |  |  |  |  |
| PA MBL |  |  |  |  |  |  |  |  |  |

\* MBL data was not recorded

We have provided SIDERO WT and SIDERO CR information on recorded MBLs for *Pseudomonas aeruginosa* and CPE. With regards to the other studies (Johnstone et al and Dobias et al) we do not hold the raw data therefore analysis by breakpoint was not possible. We have provided tables 3 and 4 detailing the breakpoints we have used to calculate the isolates in tables 1 and 2.

For Tigecycline, the MBL data was not recorded, therefore we do not have data on this comparator. The SIDERO WT and SIDERO CR study analysed aztreonam plus avibactam in combination, therefore we are unable to provide data on aztreonam alone as we are not able to extrapolate the breakpoint for a combination therapy. The remaining missing data for fosfomycin, gentamicin, amikacin and tobramycin were regimens which were not included in the study.

**Table 3 EUCAST Breakpoints:**

|  |  |
| --- | --- |
| **EUCAST Breakpoints (MIC)** |  |
| **Pseudomonas spp** |  |
| Cefiderocol | ≤2 |
| Colistin | ≤2 |
| Meropenem | ≤2 |
| **Entero spp** |  |
| Cefiderocol | ≤2 |
| Colistin | ≤2 |
| Meropenem | ≤2 |

**Table 4 CSLI Breakpoints:**

|  |  |
| --- | --- |
| **CSLI Breakpoints (MIC)** |  |
| **Pseudomonas spp** |  |
| Cefiderocol | ≤4 |
| Colistin | Colistin does not have a defined CSLI breakpoint. They do have intermediate of MIC ≤2, so for this table we have used ≤1 |
| Meropenem | ≤1 |
| **Entero spp** |  |
| Cefiderocol | ≤4 |
| Colistin | Colistin does not have a defined CSLI breakpoint. They do have intermediate of MIC ≤2, so for this table we have used ≤1 |
| Meropenem | ≤1 |