Supplementary material 1 - additional information relating to reviews and evidence

~~Appendix 2:~~ 1. Data requests

This ~~appendix~~ supplement details two data requests to Shionogi as follows:

A. Submitted to NICE on 14th June 2021 - susceptibility data contingent on susceptibility to comparators, and data relating to Merrick 2021 and CARBAR studies
B. Submitted to NICE on 11th August 2021 - Data relating to susceptibility for cefiderocol and comparators
C. Submitted to PHE on 15th June 2021 (updated version of request originally made 7th May 2021).

~~A2~~1.1. Submitted to NICE on 14th June 2021

~~A2.~~1.1.1. Susceptibility data contingent on susceptibility to comparators

We are interested in how susceptibility to cefiderocol varies according to an isolate's susceptibility to other agents. We are requesting these data for any studies reporting susceptibility that you have access to which report MBL *Enterobacterales* and MBL *Pseudomonas aeruginosa*.

For each study, please supply data separately for MBL *Enterobacterales* and MBL *Pseudomonas aeruginosa*. If possible, provide data for MBL broken down by MBL type, i.e., NDM, VIM and IMP. Please use breakpoints contemporary to the time the isolate was collected/analysed if possible, or indicate what breakpoints were used in the analysis. Please indicate which published study each data set is derived from, or if unpublished please provide patient characteristics such as mean age, gender etc and selection criteria.

We are interested in the following data:

- The proportion of isolates fully susceptible (intermediate resistance being counted as resistant) to cefiderocol amongst those not susceptible to any other drug tested.
- The proportion of isolates fully susceptible to cefiderocol amongst those only fully susceptible to colistin and/or an aminoglycoside and not to other drugs

- The proportion of isolates fully susceptible to cefiderocol amongst those fully susceptible to at least one agent that is not colistin or aminoglycosides.
- The table below indicates how the data might look for a given group e.g., MBL *Enterobacterales* (dummy data for illustration).

Grouping	**N isolates**	**% susceptible to cefiderocol**
Isolates not susceptible to any of the non-cefiderocol drugs listed in the following two rows	30	70%
Isolates susceptible to colistin and/or an aminoglycoside but not susceptible to any of the drugs listed below	100	80%
Isolates susceptible to any of the following drugs: fosfomycin, tigecycline, aztreonam, meropenem	50	90%

We would also ideally like further information on susceptibility to cefiderocol in OXA-48 (and separately for OXA-48-like) *Enterobacterales* isolates. The objective of this request is to inform the cefiderocol assessment and not the cefiderocol assessment. For any studies reporting OXA-48 *Enterobacterales* susceptibility testing we would like to understand the conditional susceptibility to cefiderocol according to the groupings above, with the following change

- The last row should change to read "Isolates susceptible to any of the following drugs: meropenem, fluoroquinolones, tigecycline, fosfomycin, cephalosporins, aztreonam, meropenem".

1. Data relating to CRO infected patients

We would like to request some further analysis of two Shionogi-funded studies (Merrick 2021, Carbar).

a) Further analysis of Merrick 2021 mortality data

Merrick 2021 presents data on all-cause mortality at 30, 60, 90 days and 1 year in Table 1.

- Please could you supply these data by site (Respiratory tract, Urinary tract, Other). If possible, please report these analyses with time zero as the start of infection.
- Please could you confirm if any patients were lost to follow up during this period and, if so, provide Kaplan Meier estimates by site (Respiratory tract, Urinary tract, Other).

Note: we are interested in patients with HAP/VAP and cUTI. We have selected respiratory tract and urinary tract infection types to approximate these infection sites. However, if there is further information that would enable patients to be classified as HAP/VAP or cUTI, please use this.

b) Further analysis of Merrick 2021 hospitalisation data

- Merrick 2021 also reports length of stay after infection and length of stay in ICU. As above, please could you supply these data by site (Respiratory tract, Urinary tract, Other). If possible, please only include days of hospitalisation/time in ICU following infection onset.
- Merrick 2021 also reports median total costs. Please could you supply *mean* total costs by site (Respiratory tract, Urinary tract, Other). If possible, please exclude costs incurred prior to infection onset.

c) Further analysis of CARBAR mortality data

CARBAR presents data on mortality for infected patients.

- Please could you provide Kaplan Meier curves for all-cause mortality by site (sputum samples, urine samples, other). If possible, please report these analyses with time zero as the start of infection and by bug (three groups: 'Stenotrophomonas', 'Pseudomonas', 'other').

Note: we are interested in patients with HAP/VAP and cUTI. We have selected sputum and urine samples to approximate these infection sites. However, if there is further information that would enable patients to be classified as HAP/VAP or cUTI please use this.

d) Further analysis of CARBAR hospitalisation data

CARBAR reports length of stay in hospital and length of stay in ICU.

- As above, please could supply these data by site (HAP/VAP and cUTI, or sputum samples, urine samples, other if HAP/VAP/cUTI not available). If possible, please only include days of hospitalisation/time in ICU following infection onset.

If possible, could evidence on length of stay in isolation and percentage requiring ventilator support also be reported by site (sputum samples, urine samples, other).

e) Baseline characteristics from CARBAR

- Please supply the following baseline characteristics (for infected patients) by site (sputum samples, urine samples, other):
  - Mean Charlson comorbidity index score and distribution of scores.
  - Proportion of patients with impaired renal function (along with details on how this is defined).
  - Mean age.

~~A2~~1.2. Submitted to NICE on 11th August 2021

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 *Enterobacterales* and *Pseudomonas aeruginosa* 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 *Enterobacterales* 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 *Enterobacterales*, 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

	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									
MBL *Enterobacterales*									
PA MBL									
SIDERO-CR									
MBL *Enterobacterales*									
PA MBL									
Johnston et al. (2020)									
MBL *Enterobacterales*									
PA MBL									
Dobias et al. (2017)									
MBL *Enterobacterales*									
PA MBL									

	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									
MBL *Enterobacterales*									
PA MBL									
SIDERO-CR									
MBL *Enterobacterales*									
PA MBL									
Johnston et al. (2020)									
MBL *Enterobacterales*									
PA MBL									
Dobias et al. (2017)									
MBL *Enterobacterales*									
PA MBL									

~~A2~~1.3. Submitted to PHE on 15th June 2021

We have several different evidential requirements, which will require different data sources / breakdowns of the data. Hence this request is broken-down by type of evidence. For all the following, we do not require a geographic breakdown (so data are requested for all of England).

1) Mechanisms of interest: changes in incidence of carbapenem-resistant gram-negative bacteria over time.

We are interested in the following five mechanism/pathogen combinations:

1. Carbapenemase-producing enterobacteriaceae (CPE) with an OXA-48 mechanism
2. CPE with a New Delhi metallo-beta-lactamase (NDM) mechanism
3. CPE with a non-NDM metallo-beta-lactamase (MBL) e.g. VIM, IMP mechanism
4. Pseudomonas with an NDM mechanism.
5. Pseudomonas with a non-NDM MBL mechanism.

If numbers are too small to split the MBL into (NDM, other), then please use MBL as a whole (which would give three mechanism/pathogen combinations).

Hence, we would like information about the number of **infections** for which the isolate is confirmed as having one of the above mechanism/pathogen combinations (we do not require any data on patients who were colonised only / tested as part of screening, although see later low-priority request). Isolates that exhibit co-existence of the above categories (if any) may be reported as a separate category or, if present in small numbers, contribute to multiple categories.

Relevant datasets:

-We would like this data from the Reference laboratory (AMRHAI) from as early as possible to current. We would ideally like this as a time-series (one per each of the three mechanism/pathogen combinations) with the smallest possible time intervals available (such as monthly or quarterly). We appreciate that numbers may be small for certain combinations, so different time intervals could be used for each combination.

-Given that the AMHRAI dataset may have an artificial drop off from 2018 and is unlikely to be nationally representative, we would like to also request this evidence from the SCGSS for the time period Oct/Dec 2020 quarter to present. This does not need to be reported as a time-series.

As a low-priority request, we are also interested in numbers of individuals colonised for the above five categories (again as a time-series - from as early as possible to current). As this is low-priority, this could be received after the other evidence that we are requesting.

2) Mechanisms of interest: changes in susceptibility patterns over time.

For isolates (infections) within each of the five mechanism/pathogen combinations listed above, we would want to know their susceptibility to the following drugs / classes of drug (where available):

1. Polymyxin (e.g. colistin)
2. Aminoglycosides
3. Cephalosporins (3rd / 4th generation, excluding ceftazidime-avibactam)
4. Ceftazidime-avibactam
5. Fluoroquinolones
6. Tigecycline
7. Fosfomycin
8. Aztreonam
9. Meropenem.
10. Cefiderocol

Again, we would like this as a time-series from AMRHAI (with different time intervals per mechanism-drug combination if needed. See first example table shell), and from the SGSS (not as a time series). For both, the time periods are the same as the previous section.

Also, if you have information on which drug(s) are tested for within each class that would be good to know.

When reporting the number of isolates that are resistant, except for meropenem, please include those isolates classified as 'intermediate' with the resistant group. For meropenem, however, we would be interested in keeping those 'intermediate' as a separate category (so three rows for meropenem)

Example table shells:

A) Resistance to a single drug:

***Enterobacterales* with OXA-48**	**Time interval 1 (e.g. January 2003, *or* 2003 Quarter 1, *or* 2003)**	**Time interval 2**	**Time interval 3**	**...etc**
Aminoglycosides: number resistant				
Aminoglycosides: number susceptible				
Fluoroquinolones: number resistant				
Fluoroquinolones: number susceptible				
...etc				

We are also interested in the proportion of isolates that exhibit multi-drug resistance. but have changed this to now request two different tables (see Shells B and C). For both, example table shells are provided, and we do not need these as time-series, so data may be pooled over time (but we would still like these separately for each five mechanism/pathogen combinations).

	Of the isolates that are resistant to the drug listed in each column…					
…the % that are susceptible to the drug listed in each row		Colistin	Aminoglycosides	Cephalosporins (exc. Caz-avi)	Ceftazidime-avibactam	Fluoroquinolones
	Colistin	-				
	Aminoglyc..		-			
	Cephalosp.. (exc. Caz-avi)			-		
	Caz-avi				-	
	Fluoroquin…					-
	Tigecycline					
	Fosfomycin					
	Aztreonam					
	Meropenem intermediate susceptible					
	Meropenem fully susceptible					
	Cefiderocol					

B) Multidrug resistance: matrix of susceptibility given resistance.

(the above table also included columns for: Tigecycline, Fosfomycin, Aztreonam, Meropenem, (intermediate resistant), Meropenem (fully resistant), and Cefiderocol

C) Multidrug resistance: categories of resistance:

Total number of isolates	Number fully susceptible to one or more of the below listed agents: • fluoroquinolones, fosfomycin, cephalosporins, aztreonam, or tigecycline (OXA-48 mechanisms only) **OR** • fosfomycin, aztreonam, or tigecycline (MBL mechanisms only) OR • meropenem (full or intermediate susceptible - all mechanisms)	Number susceptible to only colistin or an aminoglycoside	Number not susceptible to any of the previously listed drugs

If possible, we would like two versions of table shell C. One where meropenem susceptibility includes 'intermediate susceptible' and one where meropenem susceptibility excludes 'intermediate susceptible'

3) Distributions of mechanisms across clinical sites.

- We would like this information for the following pathogen/mechanisms combinations (note that there are two new categories with the inclusion of Stenotrophomonas and non-MBL

Pseudomonas and that for this we do not require the split of MBL isolates) OXA-48 *Enterobacterales*
- MBL *Enterobacterales*
- MBL Pseudomonas
- Non-MBL Pseudomonas
- Stenotrophomonas

For these mechanism/pathogen combinations we would like to know how many infections are found by clinical site (as determined by the specimen source), grouped as:

- Pneumonia.
- Complicated urinary tract infection (we understand you may have an existing definition of 'complicated', which we are happy for you to use. If not, let us know and we can try to define this).
- Other (if you can further sub-divide this by clinically meaningful sites, such as BSI, that would be useful).

This would use data from the SGSS from the Oct/Dec 2020 quarter to present. This does not need to be reported as a time-series. Hence it could be presented as a cross-tabulation (rows = mechanism, columns = site, cells = count or % whichever's easiest). See example table shell.

	Pneumonia (% or count)	**cUTI (% or count)**	**Other (% or count)**	**TOTAL across sites (n)**
OXA-48 *Enterobacterales*				
MBL *Enterobacterales*				
MBL Pseudomonas				
Non-MBL Pseudomonas				
Stenotrophomonas				

~~A2~~1.4 Further information on PHE data

As noted in the request, data come from two evidence ~~soucessources~~: AMRHAI and the SCGSS. The AMRHAI represents the longest time series of pathogen-mechanism data available to PHE and is, therefore, used to understand trends over time in numbers of individuals with the infections of interest. It is not used to inform estimates of the absolute size of the population as the reference

laboratory only receives selected samples. In addition, during 2018, guidance on which samples should be sent to AMRHAI changed, and charges were introduced. This led to an "artificial" decrease in referrals. This decrease was gradual, so it was not possible to identify an exact time-point at which temporal trends became affected by this decrease.

Cross-sectional data on the size of the HVCS population were also available from the Second Generation Surveillance System (SGSS), which is the successor to the Electronic Reporting System (ERS) (120). This is a national surveillance system. It is primarily voluntary, with varying levels of engagement from microbiology laboratories over time. In 2020, acquired carbapenemase-producing Gram-negative bacteria were added to the Health Protection Regulations, making it a legal requirement for laboratories to report these organisms to the SGSS, and reporting levels were expected to be almost complete by October 2020 (120, 121). Hence data were provided from October 2020 to March 2021 for invasive isolates. These data represent the baseline numbers of infections of interest to which the growth rates obtained from the AMRHAI time series analysis are applied. The analysis of the SGSS data includes patients both within the HVCS and in the areas of wider expected usage

Multiple AMs were included in the aminoglycoside group (amikacin, gentamicin, tobramycin) and the cephalosporin group (cefotaxime, ceftazidime, cefepime, cefpirome). Of the fluoroquinolones, there was only evidence for ciprofloxacin. The time-series data only provided data at the group level, for which results for the most resistant individual AM were used. For the isolate data results were available for each individual AM and so the preferred approach of using the most susceptible AM was used. As the time-series data were only used to inform future relative rates of change in susceptibility (not absolute levels of susceptibility) the impact of using the most resistant AM on results is expected to be negligible. For both types of data reporting for fosfomycin was very low (e.g. in the isolate-level dataset there were eight isolates with fosfomycin susceptibility data). There were concerns that this fosfomycin data may not be representative (that missing evidence was not at random), so the fosfomycin data from PHE was not used further.

Susceptibility testing was inconsistent across isolates. For example, one isolate may have only been tested for susceptibility to a single isolate, whilst another isolate may have been tested for susceptibility to all relevant comparators. Hence, to increase comparability across isolates, analyses of absolute susceptibility and susceptibility groups were restricted to isolates with full testing for all the AMs in the PICO, excluding fosfomycin (due to the paucity of reported tests for this AM). This

included testing for each of the individual AMs amongst the aminoglycosides. For the *Enterobacterales*-MBL population this resulted in 159 isolates, whilst for the *pseudomonas* population this resulted in 86 isolates.

All of the supplied data were for invasive infections only, and there was no de-duplication. In the entire dataset were 21 isolates with co-carriage of OXA-48 and an MBL. It was not possible to identify isolates with co-carriage in the analysis, so there was no removal of these.

~~Appendix 3:~~2. Data extraction fields

Data extraction fields

RCTs and Observational studies

Study details

1. Author (date) Acronym
2. Limitations (factors that may limit relevance to project research questions)

Study design

3. Study objectives
4. Study design
5. Country
6. Date of recruitment
7. Intervention
8. Comparator

Study design: population recruitment

9. Site of infection (and outcome data available by site or pathogen)
10. Inclusion criteria
11. Exclusion criteria
12. Pathogen(s) - what pathogens were eligible for inclusion. What pathogens were included
13. Mechanism(s) - what mechanisms were eligible for inclusion. What mechanisms were reported. How diagnosed
14. Any subgroups reported
15. Empiric or MD treatment in the study
16. Line of treatment

Patient characteristics

17. Patients randomised / included

Outcomes

18. Co-morbidities
19. Primary outcomes
20. Secondary outcomes
21. Adverse events

Susceptibility outcomes

22. Susceptibility population number of isolates
23. Susceptibility data
24. Susceptibility treatments tested

Resistance outcomes

25. Data unique to susceptibility

Cefiderocol susceptibility data

Study details

1. Author (date) Acronym
2. Funding
3. Country
4. Start date
5. End date

Recruitment

6. Recruitment (Consecutive or Multi-site, single-site, outbreak organism(s))
7. Definition of selection criteria
8. % meropenem resistant
9. % meropenem non-susceptible; if not meropenem, imipenem data

Mechanisms

10. MBL (mech) N
11. MIC methodology
12. Breakpoint
13. Estimated by reviewer
14. Same method and breakpoint
15. Pros
16. Cons
17. Contingent data
18. Cefiderocol

Monotherapies tested (later expanded to include susceptibility data)

19. Colistin
20. Meropenam
21. Tigecycline
22. Aztreonam
23. Fosfomycin
24. Levofloxacin
25. Ciprofloxacin
26. Gentamicin
27. Amikacin
28. Tobramycin
29. Ceftriaxone
30. Cefepime
31. Ceftazidime
32. Number of comparators

~~Appendix 5:~~3. Data sources for the susceptibility review

~~A5.~~3.1 Excluded Susceptibility and PK/PD studies with reasons.

Table 1~~140~~: Excluded Susceptibility and PK/PD studies with reasons

Number	Author (Date)	Reason for exclusion
1	Albano et al. (2020)(1)	No data reported by mechanism
2	Biagi et al. (2020)(2)	Not a relevant pathogen/mechanism.
3	Candor Simulation - Retrospective analysis of cefiderocol and comparators by population PK/PD simulation: Shionogi data on file(3)	PKD data only
4	Delgado-Valverde et al. (2020)(4)	No data on MBL mechanisms.
5	Ghazi et al. (2018)(5)	Animal model
6	Ghazi et al. (2018)(6)	Animal model
7	Golden et al. (2020)(7)	No data reported by mechanism
8	Hackel et al. (2017) SIDERO WT 2014(8)	No data reported by mechanism
9	Hackel et al. (2018)(9)	No data reported by mechanism
10	Hackel et al. (2019)(10)	Methods paper only
11	Hsueh et al. (2019)(11)	Not a relevant country (Taiwan)
12	Huband et al. (2017)(12)	Methods paper only
13	Iregui et al. (2020)(13)	No data reported by mechanism
14	Ito et al. (2018)(14)	Not a relevant pathogen/mechanism.
15	Johnston et al. (2021)(15)	Not a relevant pathogen/mechanism.
16	Karlowsky et al. (2019) SIDERO WT 2015(16)	No data reported by mechanism
17	Katsube et al (2017)(17)	PKD data only
18	Katsube et al (2017)(18)	PKD data only
19	Katsube et al (2019)(19)	PKD data only
20	Katsube et al (2019)(20)	PKD data only
21	Kawaguchi et al (2018)(21)	PKD data only
22	Kawaguchi et al (2021)(22)	PKD data only
23	Kawai et al. (2020)(23)	Not a relevant pathogen/mechanism.
24	Matsumoto et al. (2017)(24)	PKD data only
25	Nath et al. (2018)(25)	Not a relevant pathogen/mechanism

26	Paul Morris et al. (2021)(26)	No data reported by mechanism
27	Pybus et al. (2019)(27)	Biofilm data only
28	Pybus et al. (2021)(28)	Biofilm data only
29	Rolston et al. (2020)(29)	No data reported by mechanism
30	Sanabria et al. (2019)(30)	PKD & AE data only
31	Sato et al. (2020)(31)	No mechanisms of interest
32	Talan et al. (2021)(32)	No data reported by mechanism
33	Tsiplakou et al. (2017)(33)	No data reported by mechanism

AE, adverse events; MBL, metallo-beta-lactamases; PKD Pharmacokinetic or pharmacodynamic

~~A5.~~3.2 Cefiderocol susceptibility studies considered for the susceptibility synthesis with reasons for exclusion/inclusion

Table 22~~41~~: Cefiderocol susceptibility studies considered for the susceptibility synthesis with reasons for exclusion/inclusion

Author (date) Acronym	Country	Recruitment (Consecor Selected) (date)	Overall N (MBL N)	Data (MIC or %sus)	Intermediate	Breakpoint	Include in a sythesis
Included in the synthesis							
Johnston et al. (2020)(34)	US and international	Selected isolates from labs to represent all CR E.coli isolates. 2002-2017 Unclear if consecutive	343 CR ~~E.Coli~~E.coli	% sus only	I=R	CLSI, for cefi FDA criteria as of Nov 2019 (S 2 mg/liter, I or R 4 mg/liter; based on a dosage regimen of 2 g every 8 h administered over 3 h)	Yes, CLSI network only
Kazmierczak et al. (2019) SIDERO-WT 2014(35)	Europe and North America	Selected - SIDERO data 2014-2016	1272 (all mempenem non-sus CPE, PA, AB)	MIC50/90; range; %sus, for each	Yes	CLSI and EuCAST (for colistin)	Yes, as a source of methodological detail.*
SIDERO WT (data request data)(36)	Global Multi-site	Non-duplicate, non-consecutive 2014-2016	MBL: 297 (*Enterobacterales* 131; PA 166)	% Susceptible	I=R	Data reported for both ECUAST and CLSI breakpoints	Yes
Kohira et al (2016)(37)	Multinational	2 sets both selected from surveillance sets. (1 = range of paths few mechs 2009-2011; 2 = resistant 2000-2009)	850 (all *Enterobacterales*) (69)	MIC distributions - and resistance rate. (MIC50/90 or range - NR)	NR	Resistance rate CLSI breakpoints	Yes, CLSI sensitivity analysis
Longshaw et al	Europe	Selected from	870 (178)	MIC50/90; range;	No intermedia	EUCAST (except	Yes, as a source of

(2020) SIDERO CR 2014-2016(38)		SIDERO-CR surveillance collection(2014-2016)	CPE n 457; PA n 177; AB n 236.	%sus, for each	te breakpoint in EUCAST	CLSI for cefepime)	methodological detail. *
SIDERO CR (data request data)(39)	Global Multi-site	*Enterobacterales* and PA isolates from a surveillance collection with known AM susceptibility phenotypes and/or their species identification. (2014-16)	MBL: 305 (*Enterobacterales* 190; PA 115)	% Susceptible	I=R	Data reported for both ECUAST and CLSI breakpoints	Yes
Excluded from the synthesis							
Dobias et al. (2017)(40)	Multinational	Unclear, but sounds like selected to represent mechs of resistance(2000-2016 - majority 2012 -2016)	753 multi-drug resistant GN	MIC50/90; range; %sus - NR	NR	NA	No, % susceptible NR
Jacobs et al (2019)(41)	US	Selected - from collections to include carbapenem-resistant isolates	1086 CR GNE and nonfermenters	MIC50/90; range; %sus - NR	I=I but not by mech	CLSI	No, mechanism not reported for comparators.
Mushtaq et al. (2020)(42)	UK	Selected	515 (305 CPE;111 PA; 99 AB)	% at MIC 2 and 4; (no data for MIC50/90 and range)	No	Multiple	No, no comparator data for mechanisms of interest.
Kresken et al. (2020) (43)	Excluded due to low numbers (<10 isolates)						
Ito et al. (2018) (44)							

MBL, metallo-beta-lactamases; MIC50, minimum inhibitory concentration 50%; MIC90, minimum inhibitory concentration 90%; GN, Gram negative; CPE, carbapenemase-producing Enterobacterales; PA, Pseudomonas aeruginosa; AB, CLSI, Clinical Laboratory Standards Institute; NR, not reported; I, intermediate; R, resistant; * Shionogi provided data in response to a request from EEPRU which included global SIDERO-WT and global SIDERO-CR data. The global data was therefore included in preference to these publications which only included European and North American data. However, some methodological detail was retained from the

publications.

~~Appendix 8:~~4. Additional content for review 4

~~A8~~4.1 Quality assessment of Bassetti et al. 2020.

Quality assessment of the Bassetti et al. (2020)(45) systematic review was undertaken using the AMSTAR-2 (A ~~MeaSurement~~Measurement Tool to Assess systematic Reviews) critical appraisal tool for systematic reviews that include randomised or nonrandomised studies.(46) The tool comprises 16 questions that can elicit a yes, partial yes, no, or not undertaken response. The results from the AMSTAR-2 assessment, including the rationale for question responses, are presented in Table 3~~Table 347Table 47~~.

There were some issues with the quality of the review including a lack of detail about the included studies; poor reporting of the meta-analysis methodology; no assessment of the impact of risk of bias of the studies on the review findings; a lack of exploration of sources of heterogeneity and some limitations to the search strategy. Since the review did not report a meta-analysis of studies in the sites of interest in UK or European studies, and was therefore of primary use as a source of potentially relevant studies, most of the issues identified with quality were not of concern.

Some issues were identified with the robustness of the search strategy (see Table 3~~Table 347Table 47~~) in that it did not search reference lists of included studies, trail registers or grey literature, and did not contact experts. The period 2007 to present day was searched using an improved search strategy to capture any studies that may have been missed, but no additional search strategies were employed in our updated search due to time constraints.

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Table 3347: AMSTAR-2 quality assessment of the Bassetti et al. (2020) systematic review

AMSTAR-2 question	Response	Rationale
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Studies were eligible for inclusion that reported the impact of delayed appropriate antibiotic therapy for hospitalised adult patients with severe bacterial infections, including but not limited to urinary tract infections (UTIs), nosocomial pneumonia, bacteraemia, intra-abdominal infections, central nervous system infections, skin and soft-tissue infections and endocarditis. Studies were required to report the appropriateness of antibiotic therapy, an identifiable delay to initiation of appropriate therapy, and at least one of the following outcomes: mortality, treatment success, infection progression, clinical cure, microbiological eradication, duration of antibiotic treatment, hospital or intensive care unit (ICU) LoS or healthcare costs
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	The protocol detailing the review question, search strategy, inclusion and exclusion criteria, risk of bias assessment methods, and meta-analysis plane, was published on the PROSPERO database (CRD42018104669). Due to heterogeneity between studies, random-effects models were used for meta- analyses. There were no deviations from the published protocol evident in the peer-reviewed publication.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	Randomised controlled trials, non-randomised comparative studies and observational studies were eligible, but no rationale for inclusion of these study designs was reported.
4. Did the review authors use a comprehensive literature search strategy?	No	Although both MEDLINE and EMBASE were searched along with searching the reference lists of relevant systematic reviews and a citation search, there were no additional searches of the reference lists of included studies, trials registers or grey literature. There was also no consultation with topic experts to identify additional studies.
5. Did the review authors	Yes	Two reviewers independently screened the titles and

AMSTAR-2 question	Response	Rationale
perform study selection in duplicate?		abstracts for inclusion and assessed potentially relevant full-texts against the eligibility cri~~–~~teria.
6. Did the review authors perform data extraction in duplicate?	Yes	One reviewer extracted data from eligible studies using a piloted data extraction form, and a second reviewer verified every data point.
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	The review flow diagram reports that 366 articles were excluded at the full-text stage along with the number for each reason for exclusion. However, there is no table of these studies, providing the author and a citation for each of the 366 articles.
8. Did the review authors describe the included studies in adequate detail?	No	Whilst there was a narrative summary and tabulation of the interventions, outcomes, settings, and study designs, there was limited detail on the populations in the included studies.
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Risk of bias was assessed using a relevant tool (Newcastle–Ottawa scale, CRD Cohort study checklist or Cochrane risk-of-bias tool)
10. Did the review authors report on the sources of funding for the studies included in the review?	No	The sources of funding of the included studies were not reported.
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	No	Although it was reported that odds ratios were combined in a meta-analysis applying random effects, the weighting method was not reported, and subgroup or sensitivity analyses to investigate potential sources of heterogeneity were not undertaken. There was also no justification for pooling data in a meta-analysis.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	The authors did not ~~performed~~perform any analyses to investigate possible impact of risk of bias on summary estimates of effect.

AMSTAR-2 question	Response	Rationale
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No	There was no interpretation or discussion of RoB
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Heterogeneity was noted in some analyses, but there was no exploration or discussion of the sources of heterogeneity.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	A funnel plot was generated to assess publication bias among studies reporting data for the impact of appropriate versus inappropriate therapy on mortality which was deemed to be symmetrical. The authors commented that interpretation of publication bias in this way should be performed with caution, which is an acceptable summary.
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	The study was reported as being funded by Shionogi BV. Competing interests were reported.

LoS, length of stay

~~A8~~4.2 Other searches conducted

The pragmatic searches were conducted using six distinct strategies:

1. **Interrogation of the Mechanisms of Resistance database (3172 references)**. The search terms for the database comprised of terms for Mechanisms [OXA-48, NDM, VIM, IMP] AND Germ [enterobacteria, E. coli, K. pneumonia, *Pseudomonas aeruginosa*] AND Study design [Reviews, RCTs, observational studies] (see A1.3.2). Dredging of the database was conducted in two steps. First, the library was screened by searching for outcomes and infection sites of interest in the abstracts, using search terms (death or mortality or hospital) AND (cUTI or HAP or VAP). Then, the searches were repeated by searching for outcome only, following a low number of hits in the first step. The outcomes in the second step were

adjusted to (death or mortality or fatal outcome or clinical outcome) to increase the specificity of the searches, as the term 'hospital' in the first step picked up many irrelevant studies. The hits were then screened in two stages – by abstract and by full text.

2. **Interrogation of the Cost-effectiveness Models database (66 references)** created by EEPRU ~~(see Appendix 1.3.1)~~See Supplementary Material 3.~~2~~ The database was screened by abstract and by full text to identify studies previously used to model long-term outcomes of interest. Further two rounds of backward citation searches were performed on all included studies.

3. **Interrogation of the Endnote library provided by Shinogi (1261 references)**. The library was screened by searching for the following terms in the abstracts: (death or mortality or fatal outcome) AND (HAP or VAP or UTI or acute pyelonephritis). The hits were then screened in two stages – by abstract and by full text.

4. **Screening the list of key references provided by Shinogi for NICE (45 references)**. The references were screened in three steps: by title, abstract, and full text.

5. **Interrogation of the Pfizer Endnote library (81 references) and Pfizer Excel file of key papers (240 references) combined into a single Endnote library (299 references)**. The library was screened by searching for the following terms in the abstracts: (death or mortality or fatal outcome) AND (HAP or VAP or UTI or acute pyelonephritis). The hits were then screened in two stages – by abstract and by full text. Of the 299 references, 193 did not have an abstract; these were screened by title and full text.

6. **Screening the studies included in two systematic review articles provided by Shinogi (Zasowski et al., 2020; Bassetti et al., 2020)**. The reviews reported the effect of inappropriate antibiotic treatment (Zasowski 2020) and delayed antibiotic treatment (Bassetti 2020) on outcomes. The papers included in the review were screened by site, where only those that reported outcomes in HAP/VAP and cUTI were included.

The search strategies were divided between two reviewers (LS strategies 1 and 2, DJ strategies 3 - 6). Inclusion of any 'grey area' studies was determined through discussion with the wider team (BW, CR, BK).

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