Supplementary material 1 - additional information relating to reviews and evidence

1. Data requests

This appendix details two data requests to Pfizer, one to Shionogi and one to PHE as follows:

- **Submitted to NICE for the attention of Pfizer on 21st May** 2021 – request for any data relating to observational studies they may have access to IPD for
- **Submitted to NICE for the attention of Pfizer on 18th June 2021** – Any OXA-48 *Enterobacterales* susceptibility data they had access to, for CAZ-AVI and the HVCS comparators.
- **Submitted to PHE on 15th June 2021** (updated version of request originally made 7th May 2021) for evidence on susceptibility and numbers in the HVCS.

1.1 Submitted to NICE for the attention of Pfizer on 21st May 2021 – request for any data relating to observational studies they may have access to IPD for

EEPRU's data request:

*"*Our systematic review work has identified a number of small observational studies relating to the use of CAZ-AVI in patients with OXA-48, see related publications below. In order to help plan our work we were wondering whether Pfizer has access to the individual patient data for these studies or others containing OXA-48 patients and has (or is planning to), conduct any form of adjusted comparison of these data with comparator data. Given our time constraints, there would be no prospect of EEPRU agreeing and implementing data access with the lead investigators for all these studies and undertaking relevant analyses for our final reports. Therefore, any access to data or the results of analyses planned or undertaken by Pfizer would be potentially valuable."

De la Calle, Cristina, et al. "Clinical characteristics and prognosis of infections caused by OXA-48 carbapenemase-producing Enterobacteriaceae in patients treated with ceftazidime-avibactam." *International journal of antimicrobial agents* 53.4 (2019): 520-524.

Sousa, Adrian, et al. "Effectiveness of ceftazidime/avibactam as salvage therapy for treatment of infections due to OXA-48 carbapenemase-producing Enterobacteriaceae." *Journal of Antimicrobial Chemotherapy* 73.11 (2018): 3170-3175.

Temkin, Elizabeth, et al. "Ceftazidime-avibactam as salvage therapy for infections caused by carbapenem-resistant organisms." *Antimicrobial agents and chemotherapy* 61.2 (2017).

Alraddadi, Basem M., et al. "Efficacy of ceftazidime-avibactam in the treatment of infections due to Carbapenem-resistant Enterobacteriaceae." *BMC infectious diseases* 19.1 (2019): 1-6.

Castón, Juan J., et al. "Clinical efficacy of ceftazidime/avibactam versus other active agents for the treatment of bacteremia due to carbapenemase-producing Enterobacteriaceae in hematologic patients." *International Journal of Infectious Diseases* 59 (2017): 118-123.

Lim, F. H., et al. "An outbreak of two strains of OXA-48 producing Klebsiella pneumoniae in a teaching hospital." *Infection Prevention in Practice* 2.3 (2020): 100033.

Response from Pfizer received 21st June:

"We were following up internally to understand if we are able to support with the below request. Unfortunately given that the listed research studies were all independent, and not sponsored by Pfizer, we would not be able to reach out for individual patient data. Apologies that we could not be of more assistance with respects to this specific request, however, should you have any additional requests please feel free to reach out."

1.2 Submitted to NICE for the attention of Pfizer on 18th June 2021 – Any OXA-48 *Enterobacterales* susceptibility data they had access to, for CAZ-AVI and the HVCS comparators

a. EEPRU's initial data request:

We are interested in how susceptibility to caz-avi 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 OXA-48 and separately for OXA-48-like *Enterobacterales*.

Please supply data for each study separately. 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 and study 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 caz-avi amongst those not susceptible to any other drug tested.
- The proportion of isolates fully susceptible to caz-avi amongst those only fully susceptible to colistin and/or an aminoglycoside and not to other drugs.
- The proportion of isolates fully susceptible to caz-avi 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., OXA-48 *Enterobacterales* (dummy data for illustration).

Grouping	**N isolates**	**% susceptible to caz-avi**
Isolates not susceptible to any of the non-caz-avi 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: meropenem, fluoroquinolones, tigecycline, fosfomycin, cephalosporins, aztreonam, meropenem	50	90%

Pfizer's response, received 25th June 2021:

Thank you for reaching out, we have been discussing internally what data we may have that could help to support the specific request (below/attached). The challenge is that the Phase III trials of CAZ-AVI were, like other anti-infective trials, syndrome based non inferiority studies with nearly exclusive use of Carbapenem as comparator. We are exploring if any post hoc analysis has been conducted, however we need time to understand whether this is the case. It is likely, given the absolute numbers of organisms with OXA-48 activity would be extremely low, post hoc analysis may not have been deemed useful.

As such it will be difficult for us to provide the level of information you require, and in the required format.

That said, based on internal discussions we have three documents that we hope would be useful and have been uploaded to the NICE docs account;

1. **Kazmierczak KM, oxa-48 avibactam:** Paper to support the continued investigation of ceftazidime-avibactam and aztreonam-avibactam for the treatment of infections caused by carbapenem resistant Enterobacteriaceae carrying OXA-48 and OXA-48-like β-lactamases in combination with serine- or metallo-β-lactamase **[Not Confidential, no ACiC, published]**
2. **19-PZR-08_OXA-48_versus CAZ-AVI_ACiC:** Paper which covers the comparison of the activity of ceftazidime-avibactam and meropenem-vaborbactam against Enterobacterales isolates carrying blaOXA-48-like genes **[Confidential, full document is ACiC, unpublished]**
3. **Activity against OXA-48 (EU,NO,GB)_ACiC:** An internal document on the RWD capturing ceftazimdime-avibactam **[Confidential, full document is ACiC, unpublished]**

We suggest that perhaps if you could review the three documents, particularly document three and come back to us should you have any requests or questions.

a. EEPRU's data request clarification 30th June 2021

Thank you for your response to our data request.

We thought it might be worth clarifying that the types of studies that we were expecting data to come from are susceptibility studies, such as the Kazmierczak paper and Deshpande's unpublished data that you highlight. We are not interested in clinical outcomes in this data request, just in vitro susceptibility.

We were hoping for an analysis that subgroups patients according to the susceptibility profiles listed in the request, and then provides the susceptibility to caz-avi according to these groups. If you have access to the IPD data for either of these studies, we believe this analysis should be fairly straightforward. We would also be interested in analyses from any other studies you have similar IPD data for. Our reviewing work has found that the following studies were funded or part-funded by AstraZeneca and reported data for OXA-48-(Like) isolates. We assumed such studies would have been passed to Pfizer along with the marketing rights for the drug? There may also be additional studies not included in our reviewing work that contain OXA-48 isolates, which could be re-analysed to provide the relevant data, e.g. large surveillance studies.

INFORM studies	Kazmierczak 2018 (INFORM)	Kazmierczak KM, Bradford PA, Stone GG, de Jonge BL, Sahm DF. In vitro activity of ceftazidime-avibactam and aztreonam-avibactam against OXA-48-carrying Enterobacteriaceae isolated as part of the International Network for Optimal Resistance Monitoring (INFORM) global surveillance program from 2012 to 2015. Antimicrobial agents and chemotherapy. 2018 Nov 26;62(12):e00592-18.
	de Jonge 2016 (INFORM)	de Jonge BL, Karlowsky JA, Kazmierczak KM, Biedenbach DJ, Sahm DF, Nichols WW. In vitro susceptibility to ceftazidime-avibactam of carbapenem-nonsusceptible Enterobacteriaceae isolates collected during the INFORM global surveillance study (2012 to 2014). Antimicrobial agents and chemotherapy. 2016 May 1;60(5):3163-9.
	Karlowski 2019 (INFORM latin America)	Karlowsky JA, Kazmierczak KM, Bouchillon SK, de Jonge BL, Stone GG, Sahm DF. In vitro activity of ceftazidime-avibactam against clinical isolates of Enterobacteriaceae and Pseudomonas aeruginosa collected in Latin American countries: results from the INFORM global surveillance program, 2012 to 2015. Antimicrobial agents and chemotherapy. 2019 Mar 27;63(4):e01814-18
iCREST studies	Garcia-Castillo,2018 (iCREST - Spain)	García-Castillo M, García-Fernández S, Gómez-Gil R, Pitart C, Oviaño M, Gracia-Ahufinger I, Díaz-Regañón J, Tato M, Cantón R, Bou G, Rodríguez JG. Activity of ceftazidime-avibactam against carbapenemase-producing Enterobacteriaceae from urine specimens obtained during the infection-carbapenem resistance evaluation surveillance trial (iCREST) in Spain. International journal of antimicrobial agents. 2018 Mar 1;51(3):511-5.
	Giani 2020 (iCREST – Italy)	Giani T, Antonelli A, Sennati S, Di Pilato V, Chiarelli A, Cannatelli A, Gatsch C, Luzzaro F, Spanu T, Stefani S, Rossolini GM. Results of the Italian infection-Carbapenem Resistance Evaluation Surveillance Trial (iCREST-IT): activity of ceftazidime/avibactam against *Enterobacterales* isolated from urine. Journal of Antimicrobial Chemotherapy. 2020 Apr 1;75(4):979-83.

	Sherry 2018	Sherry NL, Baines SL, Howden BP. Ceftazidime/avibactam susceptibility by three different susceptibility testing methods in carbapenemase-producing Gram-negative bacteria from Australia. International journal of antimicrobial agents. 2018 Jul 1;52(1):82-5.

To illustrate the type of analysis we were hoping for, please find attached some shell data tables we hope will be useful.

Inc. carbapenems as comparators in the analsysis			Count	CAZ-AVI sus
Susceptible to a non-toxic HVCS comparator (meropenem, fluoroquinolones (levofloxacin and ciprofloxacin), tigecycline, fosfomycin, cephalosporins (ceftriaxone, cefepime, ceftazidime, exc. caz-avi), aztreonam)				
Susceptible to only colistin / aminoglycoside (gentamycin, amikacin)				
Not susceptible to any of the above				

Exc. Carbapenems as comparators			Count	CAZ-AVI sus
Susceptible to a HVCS drug (fluoroquinolones (levofloxacin and ciprofloxacin), tigecycline, fosfomycin, cephalosporins (ceftriaxone, cefepime, ceftazidime, exc. caz-avi), aztreonam)				
Susceptible to only colistin / aminoglycoside (gentamycin, amikacin)				
Not susceptible to any of the above				

Pfizer's response received 30th July 2021:

The Excel table provides a summary of the isolate susceptibility information requested from EEPRU. Omissions from the data request is Fosfomycin as we do not have any data for this. Please note this summary is based on the data held within ATLAS and is typically publicly available.

The format is not quite set out as per the shell tables suggested, however, we think this depicts the data more easily. Of note it is important to highlight that this is a summary of the global data.

With respects to the specific studies highlighted please find the information below. We have provided the data where feasible.

		Paper Summary	**Comment from Pfizer**
INFORM studies	Kazmierczak 2018 (INFORM)	Kazmierczak KM, Bradford PA, Stone GG, de Jonge BL, Sahm DF. In vitro activity of ceftazidime-avibactam and aztreonam-avibactam against OXA-48-carrying Enterobacteriaceae isolated as part of the International Network for Optimal Resistance Monitoring (INFORM) global surveillance program from 2012 to 2015. Antimicrobial agents and chemotherapy. 2018 Nov 26;62(12):e00592-18.	ATLAS data, analysis provided

	de Jonge 2016 (INFORM)	de Jonge BL, Karlowsky JA, Kazmierczak KM, Biedenbach DJ, Sahm DF, Nichols WW. In vitro susceptibility to ceftazidime-avibactam of carbapenem-nonsusceptible Enterobacteriaceae isolates collected during the INFORM global surveillance study (2012 to 2014). Antimicrobial agents and chemotherapy. 2016 May 1;60(5):3163-9.	ATLAS data, analysis provided in part for OXA-48 bugs only
	Karlowski 2019 (INFORM latin America)	Karlowsky JA, Kazmierczak KM, Bouchillon SK, de Jonge BL, Stone GG, Sahm DF. In vitro activity of ceftazidime-avibactam against clinical isolates of Enterobacteriaceae and Pseudomonas aeruginosa collected in Latin American countries: results from the INFORM global surveillance program, 2012 to 2015. Antimicrobial agents and chemotherapy. 2019 Mar 27;63(4):e01814-18	ATLAS data, analysis provided in part for OXA-48 bugs only
iCREST studies	Garcia-Castillo,2018 (iCREST - Spain)	García-Castillo M, García-Fernández S, Gómez-Gil R, Pitart C, Oviaño M, Gracia-Ahufinger I, Díaz-Regañón J, Tato M, Cantón R, Bou G, Rodríguez JG. Activity of ceftazidime-avibactam against carbapenemase-producing Enterobacteriaceae from urine specimens obtained during the infection-carbapenem resistance evaluation surveillance trial (iCREST) in Spain. International journal of antimicrobial agents. 2018 Mar 1;51(3):511-5.	Specific data not available
	Giani 2020 (iCREST – Italy)	Giani T, Antonelli A, Sennati S, Di Pilato V, Chiarelli A, Cannatelli A, Gatsch C, Luzzaro F, Spanu T, Stefani S, Rossolini GM. Results of the Italian infection-Carbapenem Resistance Evaluation Surveillance Trial (iCREST-IT): activity of ceftazidime/avibactam against *Enterobacterales* isolated from urine. Journal of Antimicrobial Chemotherapy. 2020 Apr 1;75(4):979-83.	Specific data not available
	Sherry 2018	Sherry NL, Baines SL, Howden BP. Ceftazidime/avibactam susceptibility by three different susceptibility testing methods in carbapenemase-producing Gram-negative bacteria from Australia. International journal of antimicrobial agents. 2018 Jul 1;52(1):82-5.	Specific data not available

1.3 Data request to PHE

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:

CPE 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).

B) Multidrug resistance: matrix of susceptibility given resistance.

	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					

(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 CPE
- MBL CPE
- 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 CPE				
MBL CPE				
MBL Pseudomonas				
Non-MBL Pseudomonas				
Stenotrophomonas				

1.4 Further information on PHE data

As noted in the request, data come from two evidence sources: 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

The AMRHAI data was analysed to provide estimates for the network meta-analysis. 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. The PHE data included evidence for CAZ-AVI, which is a relatively new AM. To remove any potential confounding by time when comparing the susceptibility of AMs, it was decided to first restrict the dataset to isolates which had been tested for CAZ-AVI susceptibility. This resulted in 105 isolates, of which 85 had been tested for all of the comparator AMs. 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 and the cephalosporins.

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.

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

Caz-avi 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. OXA-48 CPE N
11. OXA-48-like CPE N
12. unclear if oxa-48 or oxa-48-like
13. MBL+ OXA-48 co-carriage?
14. n/N (%) co-carriage
15. MIC methodology
16. Breakpoint
17. Estimated by reviewer
18. Same method and breakpoint
19. Pros
20. Cons
21. Contingent data
22. CAZ-AVI

Monotherapies tested (later expanded to include susceptibility data)

23. Colistin
24. Meropenam
25. Tigecycline
26. Aztreonam
27. Fosfomycin
28. Levofloxacin
29. Ciprofloxacin
30. Gentamicin
31. Amikacin
32. Tobramycin
33. Ceftriaxone
34. Cefepime
35. Ceftazidime
36. Number of comparators

3. Data sources excluded from susceptibility review

3.1 Susceptibility studies excluded on the basis of their full text (n=32)

Table 1: Studies excluded from the susceptibility sift after consulting their full text

Reason for exclusion	***Excluded studies***
No comparator data	*Alraddadi 2019*[36]
Conference abstract	*Duncan 2020*[168] *Hujer 2018*[169] *Rubio Lopez 2017*[170]
No useable data on CAZ-AVI	*Karaiskos 2021*[42] *Lyman 2015*[171] *Sahu 2020*[172] *Lopes 2020*[173]
Ten or fewer isolates	*Both 2017*[174] *Bradford 2018*[175] *Canver 2019*[176] *Giani, 2020 (iCREST - Italy)*[177] *Hujer 2020*[178] *MacVane 2014*[179] *Marshall 2017*[180] *Pragasam 2019*[181] *Satlin 2017*[182] *Senchyna 2019*[183]
No data by bug-mech	*Canton, 2021 (SMART)*[184] *Dupont 2016*[185] *Jean 2018*[186] *Jiang 2020*[187] *Katchanov 2018*[38] *Liao 2019*[188] *Woodford 2018 (iCREST - UK)*[189] *Di Domenico 2020*[190]
No all OXA-48	*Mora-Guzman 2020b*[191] *Tselepis 2020*[192]
Non-English language	*Mora-Guzman 2020a*[193]
No data on OXA-48s	*Lomovskya 2019*[194] *Niu 2020*[195]
Unclear if double counting	*Vasoo 2015*[196]

3.2 Surveillance study databases excluded from the review

The two surveillance programmes that were identified during the course of the review were also assessed.

SENTRY is a long-running (since 1997) surveillance programme which operates worldwide and is managed by JMI laboratories. An open access, searchable database is provided online. EEPRU accessed the database on 26th August 2021 and were able to retrieve data relating to 279 relevant OXA-48 *Enterobacterales* in total, but at least 262 of these reported no CAZ-AVI data. The study[45] provided by Pfizer in response to a data request by EEPRU reported a [redacted] number of OXA-48

isolates with CAZ-AVI data ([redacted], and therefore this study was included instead of data from the SENTRY database.

ATLAS also has a fully searchable open access database of isolates, and appears to draw isolates from three different surveillance programmes (TEST (Tigecycline Evaluation Surveillance Trial) surveillance program; AWARE (Assessing Worldwide Antimicrobial Resistance Evaluation); and INFORM (International Network for Optimal Resistance Monitoring) programs). EEPRU accessed the database on 4th August 2021. Pooling data from all three studies naively could underestimate between study heterogeneity, and it was not possible to retrieve data for each study separately (INFORM and AWARE could only be retrieved together). It was not clear whether the study methodologies for INFORM and AWARE were sufficiently similar to be considered the same study. The systematic review conducted by EEPRU had identified studies reporting data from INFORM.[47,54-56] To avoid the potential for double counting, and underestimating between study heterogeneity, and because more information about study methodologies was available from the published papers, data retrieved from ATLAS was not included in the review and the published sources were included instead.[47,54-56] Ultimately, one published study[56] from ATLAS was included, as detailed in ***Error! Reference source not found.***.

3.3 Studies excluded from the meta-analysis (n=12)

This section details the 12 studies that met the inclusion criteria for the review, but which were excluded from the meta-analysis, and provides the rationale for their exclusion. *Table 2* details study characteristics.

In accordance with expert advice outlined in ***Error! Reference source not found.***, three studies,[39,40,63] each relating to a separate outbreak, were excluded from the statistical synthesis since they were likely to underestimate the diversity of isolates' susceptibility profiles, and other included studies are likely to include outbreaks proportionate to their occurrence in clinical practice. Three studies[58,59,64] that tested English isolates (almost) exclusively were excluded since the data obtained from PHE was likely to include some or all of the same isolates, as collection dates overlapped, and whilst the UK published studies were larger, they reported very limited comparators (meropenem, cefepime and ceftazidime), making the PHE data the preferable source. Four[47,54-56] studies were all derived from the international INFORM surveillance programme, using different sample collection dates and locations. Since expert advice indicated that location and age of isolates were not reasons to exclude data, three data sets [47,54,55] were excluded from the analysis as they only reported data for Asia-Pacific,[54] Latin America[55] or for fewer years,[47] and the largest, which included global isolates over more years,[54] was retained. One study[49] from Greece was excluded from the analysis since it overlapped with a larger, more recent analysis.[50] Two studies[48,67] only reported MIC50 and MIC90, not % susceptibility, and whilst these

metrics, along with the reported range, could have been used to reconstruct the distribution curves and apply a breakpoint to generate an estimated % susceptibility, this was thought to introduce too much uncertainty to the estimates and the studies were therefore excluded.

Table 2: Studies that met the inclusion criteria for the review, but were excluded from the meta-analysis

Study ID Funding	*Country Multi-site? Year(s) of recruitment*	*N Includes OXA-48-like?*	*Inclusion criteria/ β-lactamase testing selection criteria*	*Consecutive sample?*	*% Mero non-susceptible*	*MBL co-carriage?*	*Laboratory methods Breakpoints*	*Source of study*	*Included in network meta-analyses?*
Excluded from meta-analysis (reported MIC50 and MIC90 but not % susceptible)									
Dobias 2017[48] Shionogi	*International*	*154* *Y*	*CPE, unclear how selected for testing*	*No, selected for "most widespread and broad spectrum resistance"*	*NR*	*NR*	*CLSI CLSI*	*EEP RU search*	*N, only reported MIC 50/90*
Delgado-Valverde, 2020[67] Shionogi	*Spain*	*57* *Unclear*	*KP, ESBL &/or carbapenemase producer, unclear how selected for testing*	*No, selected on various criteria*	*NR*	*1.8%*	*CLSI CLSI*	*EEP RU search*	*N, only reported MIC 50/90*
UK studies excluded from meta-analysis due to overlap with PHE data									
Livermore 2018[58] PHE & MSD	*UK (PHE), 1%, International, multi-site 2015-16*	*333* *Y*	*CPE isolates submitted to PHE AMRHAI with suspected CR*	*Unclear*	*NR*	*NR*	*BSAC EUCAST*	*EEP RU search*	*N - overlap with PHE dataset*
Mushtaq 2021[64] Wockhardt Ltd	*UK (PHE), multi-site 2015-16*	*250* *274* *Y*	*CPE isolates submitted to PHE AMRHAI with suspected CR*	*Unclear*	*27.2%*	*0%* *8.75%*	*BSAC* *EUCAST*	*EEP RU search*	*N - overlap with PHE dataset*
Livermore 2017a[59] Wockhardt Ltd	*UK (PHE), multi-site NR*	*15* *Y*	*CPE (isolates submitted to PHE AMRHAI with suspected CR +*	*Unclear*	*86.7%*	*NR*	*CLSI* *EUCAST*	*EEP RU search*	*N - overlap with PHE dataset*

Study ID Funding	*Country Multi-site? Year(s) of recruitment*	*N Includes OXA-48-like?*	*Inclusion criteria/ β-lactamase testing selection criteria*	*Consecutive sample?*	*% Mero non-susceptible*	*MBL co-carriage?*	*Laboratory methods Breakpoints*	*Source of study*	*Included in network meta-analyses?*
			resistance surveys (unclear how selected for testing))						
Studies excluded to avoid double counting of isolates									
de Jonge 2016 (INFORM)[47] AztraZeneca	*International, multi-site 2012-2016*	*134 Y*	*CPE, Meropenem non-susceptible tested*	*Assume same as Kazmierczak 2018[56]*	*100%*	*0%*	*CLSI CLSI, EUCAST col, FDA TIG, CAZ-AVI*	*EEP RU search*	*N, overlap with Kazmierczak 2018[56]*
Karlowsky 2019 (INFORM latin america)[55]	*Latin America, multi-site 2012-2015*	*14 Y*	*CPE - CR or ceftazidime-resistant, or positive for ESBL by clavulanic acid testing*	*No - Selected predefined # per species*	*14.3%*	*unclear*		*EEP RU search*	
Karlowsky 2018 (INFORM Asia-Pacific)[54]	*Asia-Pacific*	*Data extraction not performed as n<10. Reported here as relates to INFORM study.*						*EEP RU search*	*N, overlap with Kazmierczak 2018[56] N<10*
Galani 2018[49]	*Greece, multi-site 2014-16*	*14 Y*	*CR KP, non-suscepitlbe to any carbapenem were tested*	*Y*	*100%*	*0%*	*CLSI EUCAST*	*EEP RU search*	
Outbreaks									
Lim 2020[39] NR	*UK, single-site 2018*	*60 Unclear*	*KP OXA-48 outbreak, then all medical*	*Y*	*10%*	*NR*	*EUCAST EUCAST*	*EEP RU search*	*N, outbreak study*

Study ID Funding	*Country Multi-site? Year(s) of recruitment*	*N Includes OXA-48-like?*	*Inclusion criteria/ β-lactamase testing selection criteria*	*Consecutive sample?*	*% Mero non-susceptible*	*MBL co-carriage?*	*Laboratory methods Breakpoints*	*Source of study*	*Included in network meta-analyses?*
			wards were screened (not all screened were KP)						
Sousa 2018[40] Internal hospital funding	*Spain, single-site 2016-17*	*57 Unclear*	*KP-outbreak*	*Y*	*98%*	*NR*	*CLSI CLSI*	*EEP RU search*	*N, outbreak study*
Mavroidi 2020[63]	*Greece, single-site 2014-2016*	*23 Unclear*	*KP outbreak, then retrospective screening of frozen isolates and testing of colistin-resistant isolates*	*Y*	*0%*	*0%*	*CLSI CLSI, EUCAST for colistin and TIG*	*EEP RU search*	*N, outbreak study*

Col, colistin; CPE, carbapenemase-producing *Enterobacterales*; TIG, tigecycline; CAZ-AVI ceftazidime-avibactam; Chemotherapy; CLSI, Clinical Laboratory Standards Institute; CPE, carbapenemase-producing *Enterobacterales*; DoH, department of health; EUCAST, European Committee on Antimicrobial Susceptibility Testing; KP, Klebsiella pneumonae; Mero, meropenem; MBL, metallo-β-lactamase; N, No; Y, yes

4. Additional content for review 4

4.1 Quality assessment of Bassetti *et al*. 2020.

Quality assessment of the Bassetti *et al*. (2020)[83] systematic review was undertaken using the AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews) critical appraisal tool for systematic reviews that include randomised or nonrandomised studies.[197] 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.

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*) 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.

Table 3: 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*	*RCTs, 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 perform study selection in duplicate?	*Yes*	*Two reviewers independently screened the titles and 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.*

AMSTAR-2 question	*Response*	*Rationale*
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 any analyses to investigate possible impact of risk of bias on summary estimates of effect.*
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.*

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, P. aeruginosa] AND Study design [Reviews, RCTs, observational studies] (see *Appendix 1.3.2*). 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. 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).