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1 **Global prevalence of cefiderocol non-susceptibility in Enterobacterales, Pseudomonas**
2 **aeruginosa, Acinetobacter baumannii and Stenotrophomonas maltophilia: a systematic**
3 **review and meta-analysis**

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26 **Abstract**

27 **Background:** Cefiderocol is a last resort option for carbapenem-resistant (CR) Gram-negative
28 bacteria, especially metallo- β -lactamase (MBL)-producing *Pseudomonas aeruginosa* and CR
29 *Acinetobacter baumannii*. Monitoring global levels of cefiderocol non-susceptibility (CFDC-NS) is
30 important.

31 **Objectives:** To systematically collate and examine studies investigating in-vitro CFDC-NS and
32 estimate the global prevalence of CFDC-NS against major Gram-negative pathogens.

33 **Data sources:** PubMed and Scopus, up to May 2023.

34 **Study eligibility criteria:** Eligible were studies reporting CFDC-NS in Enterobacterales, *P. aeruginosa*,
35 *A. baumannii*, or *Stenotrophomonas maltophilia* clinical isolates.

36 **Methods:** Two independent reviewers extracted study data and assessed risk of bias on the
37 population, setting and measurement (susceptibility testing) domains. Binomial-Normal mixed-
38 effects models were applied to estimate CFDC-NS prevalence by species, co-resistance phenotype
39 and breakpoint definition (EUCAST, CLSI, FDA). Sources of heterogeneity were investigated by
40 subgroup and meta-regression analyses.

41 **Results:** In all, 78 studies reporting 82,035 clinical isolates were analysed (87% published between
42 2020 and 2023). CFDC-NS prevalence (EUCAST breakpoints) was low overall, but varied by species [*S.*
43 *maltophilia* 0.4% (95%CI 0.2-0.7%), Enterobacterales 3.0% (95%CI 1.5-6.0%), *P. aeruginosa* 1.4%
44 (95%CI 0.5-4.0%)] and was highest for *A. baumannii* (8.8%, 95%CI 4.9-15.2%). CFDC-NS was much
45 higher in CR Enterobacterales (12.4%, 95%CI 7.3-20.0%) and CR *A. baumannii* (13.2%, 95%CI 7.8-
46 21.5%), but relatively low for CR *P. aeruginosa* (3.5%, 95%CI 1.6-7.8%). CFDC-NS was exceedingly
47 high in NDM-producing Enterobacterales (38.8%, 95%CI 22.6-58.0%), NDM-producing *A. baumannii*
48 (44.7%, 95%CI 34.5-55.4%), and ceftazidime/avibactam-resistant Enterobacterales (36.6%, 95%CI
49 22.7-53.1%). CFDC-NS varied considerably with breakpoint definition, predominantly among CR

50 bacteria. Additional sources of heterogeneity were single-centre investigations and geographical
51 regions.

52 **Conclusions:** CFDC-NS prevalence is low overall, but alarmingly high for specific CR phenotypes
53 circulating in some institutions or regions. Continuous surveillance and updating of global CFDC-NS
54 estimates are imperative while cefiderocol is increasingly introduced into clinical practice. The need
55 to harmonize EUCAST and CLSI breakpoints was evident.

56

57 **Key words:**

58 Cefiderocol; drug resistance; carbapenem-resistant; gram-negative bacteria; prevalence; global
59 epidemiology.

60

61 Introduction

62

63 Pandrug-resistant Gram-negative bacteria (GNB) are increasingly being reported worldwide
64 [1] and are associated with significant mortality [2] and limited treatment options [3, 4]. Among the
65 currently available antimicrobials, cefiderocol is a last resort option, especially for carbapenem-
66 resistant (CR) *Acinetobacter baumannii* and metallo- β -lactamase (MBL)-producing *Pseudomonas*
67 *aeruginosa*, since newer β -lactam- β -lactamase inhibitors (including ceftazidime/avibactam \pm
68 aztreonam, ceftolozane/tazobactam, meropenem/vaborbactam and imipenem/relebactam) are
69 inactive against these pathogens [3, 5].

70 However, as with any new drug, resistance to cefiderocol is increasingly being reported and
71 even preceded its clinical use [6, 7]. Notably, cefiderocol heteroresistance is widespread [8] and
72 could potentially result in emergence of resistance in-vivo during treatment [6] and eventually
73 spread of cefiderocol-resistant strains within and across institutions and geographical regions.
74 Furthermore, various β -lactamases have been reported to significantly reduce cefiderocol
75 susceptibility [6]. Among MBLs, New Delhi metallo- β -lactamase (NDM) appears to be the most likely
76 contributing source to cefiderocol resistance [6, 7]. Ceftazidime/avibactam-resistant isolates are also
77 more likely to be cefiderocol-resistant, either due to being MBL-producing or due to *Klebsiella*
78 *pneumoniae* carbapenemase (KPC) variants conferring cross resistance to cefiderocol [6].

79 This systematic review and meta-analysis aimed to estimate the global prevalence of
80 cefiderocol non-susceptibility (CFDC-NS) in Enterobacterales, *P. aeruginosa*, *A. baumannii* and
81 *Stenotrophomonas maltophilia*, including subgroups of problematic co-resistance phenotypes
82 (carbapenem-resistant, MBL-producing, NDM-producing, ceftazidime/avibactam-resistant and
83 ceftolozane/tazobactam-resistant). In addition, concurrent analyses of different susceptibility
84 breakpoint thresholds (proposed by CLSI [9], FDA [10], and EUCAST [11]) were performed, and
85 variation of CFDC-NS prevalence with study-level characteristics was examined.

86 **Methods**

87

88 **Protocol**

89 This review was registered with the International Prospective Register of Systematic Reviews
90 (registration no. CRD42021265927) and complies with the Preferred Reporting Items for Systematic
91 Reviews and Meta-Analyses guidelines [12].

92

93 **Search strategy, information sources and eligibility criteria**

94 PubMed and Scopus were queried from inception to May 27, 2023, with the search term
95 “cefiderocol OR s-649266”, without language restriction. After de-duplication, retrieved articles
96 were screened for eligibility by one author using the Rayyan online app for collaborative systematic
97 reviews [13]. A second author validated eligibility of included articles.

98 Eligible for review were studies of any type of primary research design if they reported
99 cefiderocol susceptibility proportions of clinical isolates of Enterobacterales, *P. aeruginosa*, *A.*
100 *baumannii* and/or *S. maltophilia*. Exclusion criteria were (in order they were applied): (1) non-
101 primary research articles (e.g. commentaries, editorials, review articles); (2) in vivo infection models
102 in animals; (3) case reports of a single isolate or consecutive isolates from a single patient, (4) studies
103 of selected non-consecutive and/or non-random isolates that could result in selection bias when
104 estimating cefiderocol susceptibility (e.g. isolates selected based on cefiderocol resistance, or studies
105 of patients selected based on receiving treatment with cefiderocol, or series of non-consecutive non-
106 random isolates selected based on specific resistance phenotypes), including experimental studies
107 and randomized controlled trials; (5) irrelevant primary research articles without data of interest to
108 this review (e.g. pharmacokinetic/pharmacodynamic, toxicology studies, non-clinical isolates); and
109 (6) conference abstracts.

110

111 **Data collection process**

112 Full text papers for all eligible studies were obtained and two reviewers extracted data
113 independently using a purpose-built spreadsheet that had been piloted on two eligible studies by all
114 authors. Data extraction from articles written in languages other than English was done with the aid
115 of Google Translate. The following information was extracted from each paper, when provided:
116 geographical location (country or countries) where the study was conducted, number of
117 participating institutions, breakpoint cut-off used to define resistance, methods of susceptibility
118 testing, numbers and proportions of CFDC-NS isolates for each pathogen species, minimum inhibitor
119 concentration (MIC) range, MIC50 and MIC90. Bacterial subgroups of interest were carbapenem
120 (CAR)-resistant Enterobacterales, MBL-producing Enterobacterales, NDM-producing
121 Enterobacterales, ceftazidime/avibactam (CZA)- and ceftolozane/tazobactam (CTA)- resistant
122 Enterobacterales, CR *P. aeruginosa*, MBL-producing *P. aeruginosa*, NDM-producing *P. aeruginosa*,
123 CZA- and CTA-resistant *P. aeruginosa*, CR *A. baumannii*, MBL-producing *A. baumannii* and NDM-
124 producing *A. baumannii*.

125 Overlapping studies reporting duplicate isolates were detected by contrasting information
126 on institutions, authors and periods when the studies were conducted. Some studies contributed
127 more than one set of clinical isolates in different periods, at different institutions/regions, and/or for
128 different co-resistance phenotypes. Such subsets were analysed as separate studies in the meta-
129 analyses.

130

131 **Methods of susceptibility testing**

132 Broth microdilution (BMD) in iron-depleted cation-adjusted Mueller-Hinton broth (ID-
133 CAMHB) (prepared according to recommendations by CLSI [9] or EUCAST [14]) is the currently
134 preferred method for evaluating susceptibility to cefiderocol [9, 11, 15, 16]. ID-CAMHB preparation
135 using human apotransferrin is not recommended due to MIC reproducibility issues [14]. Disk
136 diffusion in standard MH agar (iron-depletion not necessary because iron is bound by the medium) is

137 an alternative, but not recommended for *A. baumannii* [16] and resistance detected by disk
138 diffusion should ideally be confirmed by broth microdilution [17]. Colonies within zone should be
139 taken into account when measuring the zone diameter [15]. In case of studies reporting more than
140 one method, data extraction was based on the following (in order of preference): broth
141 microdilution, disk diffusion, gradient strip. Susceptibility breakpoints for cefiderocol vary.
142 Contemporary breakpoints proposed by FDA [10], CLSI [9] and EUCAST [11] are summarized in the
143 [Supplement \(Section 1\)](#). With respect to EUCAST, non-species related PK/PD-based breakpoints were
144 applied for *A. baumannii* and *S. maltophilia*. In studies reporting a single criterion, susceptibility
145 percentages for other breakpoint criteria were inferred based on reported MIC ranges or MIC
146 distribution data when available (when maximum MIC was below the susceptibility breakpoint a 0%
147 non-susceptibility was inferred).

148

149 **Definitions of co-resistance phenotypes**

150 Underlying co-resistance phenotypes were categorized as any phenotype, CR, MBL-
151 producing, NDM-producing, CZA-resistant, or CTA-resistant. “Any phenotype” referred to studies
152 with non-selected isolates of mixed resistance phenotypes. Studies selecting isolates solely based on
153 being CR or CZA-resistant or CTA-resistant or MBL-producing, were reported separately from the
154 “any phenotype” category to avoid overestimating CFDC-NS prevalence, which was expected to be
155 higher for those phenotypes [6]. Similarly, studies selecting isolates solely based on being CZA-
156 resistant, CTA-resistant or MBL-producing isolates were reported separately from the CR category,
157 whereas studies selecting solely NDM-producing isolates were reported separately from the MBL
158 category. Depending on data availability and definitions in the studies, CR was defined, in order of
159 preference, as meropenem MIC>8mg/L, or meropenem resistance or non-susceptibility according to
160 another study-defined breakpoint, or non-susceptibility as defined in the study (not necessarily
161 based on meropenem), or carbapenemase-production.

162

163 **Risk of bias assessment**

164 Two reviewers examined independently each study for risk of bias concerning two main
165 domains applicable to this review [18]: (a) population and setting and (b) condition measurement
166 (validity and standardization of the susceptibility testing method). Discrepancies in risk of bias
167 assessments were resolved by discussion and consensus. Items for each domain were adapted from
168 the Joanna-Briggs critical appraisal tool for prevalence studies [18, 19]. Items and their
169 interpretation as used in this review are described in the [Supplement \(Section 2\)](#). Studies at
170 moderate or high risk of bias in either domain were categorized as moderate-to-high risk overall,
171 while studies at low risk of bias in both domains were categorized as low risk of bias overall.

172

173 **Meta-analysis methods**

174 The primary outcome for meta-analysis was CFDC-NS prevalence, stratified by combinations
175 of microorganism species, definition of breakpoints and underlying co-resistance phenotype.
176 Population-averaged proportions were estimated using a random intercept logistic regression model
177 with maximum likelihood estimation [20]. The model assumed a Binomial distribution for the
178 observed number of CFDC-NS isolates in each study and a Normal distribution for the random
179 population-level effects following the logit transformation. This approach correctly handles
180 proportions near 0% or 100% (when variance tends towards zero and classic inverse variance
181 weights are problematic), [21] and maintains the confidence limits of pooled proportions within the
182 zero to one range. The resulting confidence interval (CI) contains highly probable values for the
183 population-averaged (pooled) prevalence proportion of CFDC-NS.

184 Higgin-Thompson's I^2 statistic was used as a summary index of the amount of variability of
185 CFDC-NS proportions across studies that cannot be attributed to sampling error. Because I^2 is usually
186 high and may not be discriminative for prevalence data [22], we additionally reported between-
187 study variance (τ^2) with respective 95% prediction interval (PI). The PI describes the range CFDC-NS
188 proportions that can be expected in new studies or settings [23]. We used summary forest plots to

189 present pooled estimates with heterogeneity statistics for each microorganism and each different
190 combination of breakpoint threshold with co-resistance phenotype. Additionally, we constructed
191 forest plots for the study-specific data used in each meta-analysis to illustrate the distributions of
192 CFDC-NS proportions across the studies along with 95% CIs calculated by Wilson's score method
193 (presented in the [Supplement](#)).

194 To examine potential sources of variation in CFDC-NS prevalence, we conducted a series of
195 univariate meta-regressions with the Binomial-Normal mixed-effects model. We applied this to
196 carbapenem-resistant *Enterobacteriales*, *P. aeruginosa*, *A. baumannii* and *K. pneumoniae* based on
197 the CLSI breakpoints, as this was the most frequent combination of breakpoints with co-resistance
198 phenotype with a minimum of 15 studies available for each meta-regression. Odds ratios (ORs) with
199 respective 95% CI were calculated to summarise the strength and direction of associations between
200 study-level covariates and CFDC-NS prevalence. A covariate-specific R^2 was calculated as the portion
201 of between-study variance that was reduced after the inclusion of that covariate in a null model.
202 Moreover, for each covariate level we calculated pooled estimates of CFDC-NS prevalence based on
203 subgroup analysis. Candidate covariates were decided a priori in our study protocol. The following
204 study-level variables were examined: year when data collection ended, geographical region (WHO
205 classification), multinational setting (yes/no), multicentre setting (yes/no), and risk of bias (classified
206 as either low or moderate-to-high). Despite our protocol plans, we were unable to examine
207 substantive characteristics related to clinical setting (such as type and level of care, age of the
208 patients, clinical specialty, and type of infection), which were largely unreported in the studies. The
209 number of retrieved studies was inadequate to justify multivariable meta-regression.
210 All analyses were carried out in STATA (Version 17; Statcorp, College Station, TX, USA).

211

212 **Results**

213

214 **Study characteristics**

215 The flow chart of the review is depicted in [Figure 1](#). A total of 78 studies were eligible for
216 review [8, 16, 21, 24-98], which contributed 86 independent sets of data for analysis and reported
217 82,035 clinical isolates in total. Main characteristics of the studies are summarized in the
218 [Supplement, Sections 3-6](#). Several studies were identified as having overlapping collections of
219 isolates as a result of the SIDERO-WT surveillance study being conducted yearly (2014-2019) in
220 several countries in North America and Europe [25, 26, 55, 56, 58, 99-105]. Only non-overlapping
221 data were collected for meta-analysis (see [Supplement, Section 7](#)). Most studies (87%) were
222 published in the last four years (2020-2023). Regions most represented were Europe (50% of data
223 sets), the Americas (33%), and the Western Pacific Region (17%) ([Supplement, Section 5](#)). Data for
224 Enterobacterales were reported in 53 studies [8, 16, 26-31, 33, 34, 36-38, 41-48, 51, 54, 56, 57, 59,
225 60, 62, 64-69, 72, 75-85, 87, 91, 92, 95, 96], *P. aeruginosa* in 41 studies [7, 8, 16, 26, 28, 33, 34, 36,
226 39, 41-43, 45-49, 52-54, 56, 57, 61, 63, 66, 70, 71, 73-75, 78, 79, 83, 85, 86, 88, 89, 91, 94, 97, 106],
227 *A. baumannii* in 35 studies [8, 16, 24, 26, 28, 30, 33-36, 39, 41-43, 45-48, 50, 52-54, 56, 57, 61, 66,
228 75, 78, 79, 85, 86, 90, 91, 93, 107] and *S. maltophilia* in 19 studies [8, 16, 26, 28, 30, 33, 40-42, 48,
229 52-54, 61, 74, 75, 78, 79, 85].

230

231 **Risk of bias assessment**

232 Overall risk of bias was moderate-to-high in most (94%) study sets of data, predominantly
233 concerning moderate or high risks in the population and setting domains (86% of data sets). The
234 latter was mostly due to inadequate descriptions of the characteristics of the study populations and
235 insufficient sample sizes in individual studies of the pathogen populations of interest ([Supplement,](#)
236 [Section 6](#)). About half (n=46; 54%) of the study sets were classified as moderate-to-high risk of bias
237 in the domain of condition measurement. In about half of the cases (n=44, 51%), the studies lacked a
238 clear definition or citation of the method for interpreting trailing (broth microdilution) or colonies
239 within zone (disk diffusion). There were 14 data sets for which a method other than broth

240 microdilution was used (n=9 disk diffusion [8, 36, 37, 51, 65, 72, 75, 88, 92, 95], n=5 gradient strip
241 [36, 68, 69, 94, 97]). Apotransferrin for medium preparation was reported on 4 data sets (2 studies
242 [60, 61]).

243

244 **Cefiderocol activity against Enterobacterales**

245 [Figure 2](#) is a summary forest plot of CFDC-NS prevalence estimates in Enterobacterales for
246 different combinations of breakpoints definition and co-resistance phenotype. The respective forest
247 plots for each separate meta-analysis and a summary table are available in [the Supplement \(Section](#)
248 [8\)](#). Data on CFDC-NS against the various Enterobacterales species (*Klebsiella* spp, *E. coli*,
249 *Enterobacter* spp, *Serratia* spp, *Citrobacter* spp, *Proteus* spp, *Morganella morganii*) are also available
250 in the [Supplement \(Section 9\)](#).

251 Using the EUCAST breakpoint thresholds, the pooled CFDC-NS prevalence was generally low
252 (3.0%, 95% CI 1.5-6.0%), but much higher in CR Enterobacterales (12.4%, 95% CI 7.3-20.0%), and
253 exceedingly high in MBL-producing (24.9%, 95% CI 16.6-35.5%), NDM-producing (38.8%, 95% CI
254 22.6-58.0%) and CZA-resistant (36.6%, 95% CI 22.7-53.1%) Enterobacterales. Notable differences in
255 CFDC-NS percentages were evident when contrasting the results between the EUCAST breakpoints
256 and the CLSI breakpoints in [Figure 2](#). Pooled CFDC-NS percentages based on the former were much
257 greater than the latter, especially among CR (12.4% vs 3.8%), MBL-producing (24.9% vs 13.0%),
258 NDM-producing (38.7% vs 18.7%) and CZA-resistant (36.6% vs 8.3%) Enterobacterales.

259

260 **Cefiderocol activity against *P. aeruginosa***

261 As seen in [Figure 3](#), CFDC-NS prevalence (EUCAST breakpoints) was generally low (1.4%, 95%
262 CI 0.5-4.0%), even among CR (3.5%, 95% CI 1.6-7.8%), and MBL-producing (1.8%, 95% CI 0.3-10.4%),
263 CZA-resistant (6.8%, 95% CI 3.1-14.6%) and CTA-resistant (8.3%, 95% CI 4.1-16.0%) isolates. CFDR-NS
264 proportion was highest among NDM-producing isolates (22.9%, 95% CI 8.1-49.7%) but this estimate
265 was based on few isolates (n=51). Notable differences in CFDC-NS prevalence estimates were

266 observed comparing CLSI to EUCAST and FDA definitions of breakpoints among the CR *P. aeruginosa*
267 isolates (0.8% vs 3.5% vs 14.6%), especially for the MBL-producers (1.6% vs 1.8% vs 23.3%), NDM-
268 producers (19.5% vs 22.9% vs 58.7%), CZA-resistant (1.7% vs 6.8% vs 19.5%) and CTA-resistant (2.2%
269 vs 8.3% vs 15.1%) isolates. The respective forest plots for each meta-analysis of each combination of
270 breakpoint criterion and co-resistance phenotype, together with a summary table, are available in
271 the [Supplement \(Section 10\)](#).

272

273 **Cefiderocol activity against *A. baumannii***

274 The summary forest plot of subgroup-averaged proportions of CFDC-NS against *A. baumannii*,
275 by co-resistance phenotype and breakpoints definition, is depicted in [Figure 4](#). Respective forest
276 plots for each meta-analysis and summary table are available in the [Supplement \(Section 11\)](#). Overall
277 CFDC-NS prevalence in *A. baumannii* was higher compared to other species. CFDC-NS proportions
278 (EUCAST breakpoints) were similar in the “any phenotype” (8.8%, 95% CI 4.9-15.2%,) and the CR
279 (13.2%, 95% CI 7.8-21.5%) groups of *A. baumannii*, reflecting the high burden of carbapenem-
280 resistance in this organism (i.e. sets of non-selected isolates classified as any/mixed phenotype
281 included large portions of CR isolates). CFDC-NS prevalence was much higher among MBL-producing
282 (40.9%, 95% CI 31.4-51.1%) and NDM-producing (44.7%, 95% CI 34.5-55.4%) *A. baumannii* isolates,
283 with the majority of MBL-producing isolates being NDM-producers. Similar to other species, CFDC-
284 NS prevalence was much lower when CLSI breakpoints were used as opposed to the EUCAST and
285 FDA cut-offs among CR *A. baumannii* isolates (8.5% vs 13.2% vs 26.6%, respectively), especially for
286 the MBL-producers (20.4% vs 40.9% vs 53.1%) and the NDM-producers (23.0% vs 44.7% vs 71.3%,
287 respectively).

288

289 **Cefiderocol activity against *S. maltophilia***

290 Cefiderocol non-susceptibility against *S. maltophilia* was very low, irrespective of the
291 breakpoint definition used. CFDC-NS prevalence was 0.2% (95% CI 0.1-0.4%) where earlier CLSI

292 breakpoint criteria were used, 0.1% (95% CI 0.0-3.7%) when the new CLSI criteria were used, and
293 0.4% (95% CI 0.2-0.7%) with EUCAST breakpoints. In the largest study contributing the majority of
294 data for *S. maltophilia*, the prevalence of CFDC-NS was 2.4% based on the new CLSI breakpoints,
295 compared to 0.4% based on EUCAST and 0.2% based on prior CLSI breakpoints. A summary forest
296 plot and respective forest plots for each meta-analysis are available in the [Supplement \(Section 12\)](#).

297

298 **Heterogeneity**

299 As evident from the heterogeneity statistics and prediction intervals in [Figures 2-4](#), the data
300 were characterised by considerable variability, even within the subgroups defined by combinations
301 of co-resistance phenotype and breakpoint definition. Potential sources of variation in CFDC-NS
302 prevalence were examined among CR isolates (CLSI breakpoints) by a series of univariate meta-
303 regressions and the results are presented in the [Supplement \(Section 13\)](#). Indicatively, we present
304 the results of the investigation for Enterobacterales in [Table 1](#). These investigations revealed that
305 single-centre study designs were associated with higher CFDC-NS prevalence, explaining a large
306 portion of the variance among Enterobacterales (R^2 28%) and *A. baumannii* (R^2 21%). Regional
307 variation was also observed. The results also suggested, albeit with a high degree of uncertainty,
308 that CFDC-NS prevalence was higher in the Americas than elsewhere for CR *K. pneumoniae* (OR 1.9;
309 95% CI 0.2 - 17.4), higher in the Western Pacific Region than elsewhere for CR Enterobacterales (OR
310 3.3; 95% CI 0.4 – 27.0) and higher in Europe than elsewhere for CR *P. aeruginosa* (OR 1.6; 95% CI 0.3
311 – 9.6). Consistently in all meta-regressions, there was no evidence of variation in CFDC-NS
312 prevalence according to risk of bias assessments.

313

314 **Discussion**

315

316 This systematic review and meta-analysis revealed differential pathogen-specific variation in the
317 global prevalence of CFDC-NS, which was seen to be low for Enterobacterales, *P. aeruginosa*, and *S.*
318 *maltophilia* but much higher against *A. baumannii*. Significant variability was also observed within
319 each species, depending on the underlying antimicrobial co-resistance phenotype. Overall,
320 cefiderocol appeared to retain relatively good activity against CR bacteria (especially CR *S.*
321 *maltophilia* and *P. aeruginosa*), but for certain phenotypes (MBL/NDM-producing Enterobacterales
322 and *A. baumannii*, and CZA-resistant Enterobacterales) CFDC-NS is exceedingly high.

323 Substantial heterogeneity of CFDC-NS prevalence among the studies was highlighted in this
324 review and was found to persist even within presumably homogeneous subgroups of isolates
325 defined by different combinations of co-resistance phenotype and CFDC breakpoint threshold. There
326 was some evidence of regional variation, which might reflect differences in the epidemiology of
327 carbapenemases between the regions, with selected carbapenemases having conferred cross-
328 resistance to CFDC [6]. In addition, antimicrobial resistance might vary significantly among different
329 clinical settings, but despite our initial plans, relevant data were largely unreported in the studies.
330 Therefore, the population-averaged susceptibility estimates reported in this study are probably not
331 generalizable to individual institutions and/or specific clinical settings (as indicated by wide
332 prediction intervals), but serve to illustrate that despite high susceptibility to cefiderocol overall,
333 there are settings where high non-susceptibility has been reported. Notably, the meta-regression
334 models consistently attributed higher odds of CFDC-NS to single-centre studies. This might reflect
335 clonal spreads or outbreaks of CR clones, possibly associated with β -lactamases, that have resulted
336 in decreased cefiderocol susceptibility locally in some institutions or regions. Nevertheless, the lower
337 prediction limits of CFDC-NS prevalence were considerably higher than zero for several co-resistance
338 phenotypes examined in this review; thereby a high index of suspicion should be maintained when
339 empirically administering cefiderocol, particularly in settings of aggravated antimicrobial resistance,
340 or when *A. baumannii* is implicated.

341 Cefiderocol, exhibiting greater stability against β -lactamases (ESBL, AmpC, and all classes of
342 carbapenemases including MBLs) can inhibit (especially based on CLSI breakpoints) the vast majority
343 of Gram-negative isolates that are not-susceptible to carbapenems, ceftazidime/avibactam,
344 ceftolozane/tazobactam and colistin [54, 58, 108, 109]. However, despite very high susceptibility
345 rates in initial reports worldwide, non-susceptibility to cefiderocol appears to be more common in
346 CR Gram-negative pathogens when applying the more stringent breakpoints proposed by EUCAST or
347 FDA (the latter for non-fermenting Gram-negative bacteria) [16, 47]. In line with the current meta-
348 analysis, a prior systematic review on mechanisms of CFDC-NS by the same authors, identified
349 several β -lactamases (and various other mechanisms) that may result in higher MIC of cefiderocol,
350 notably NDM and KPC variants conferring resistance for CZA [6]. Of interest, combination of
351 cefiderocol with β -lactamases may be able to overcome resistance [6, 110].

352 Significant differences in the levels of CFDC-NS prevalence were noted when different proposed
353 thresholds for antimicrobial breakpoints were used, which were pronounced among the CR
354 phenotypes, especially MBL/NDM-producing isolates, similar to a previous report [111]. This has
355 important clinical implications as the greatest clinical utility of cefiderocol is against infections by CR
356 Gram-negative bacteria, particularly the MBL-producing isolates, which are associated with limited
357 treatment options [3]. Therefore, harmonization of breakpoints is urgently needed, as well
358 development of accurate in vitro susceptibility testing considering limitations of current methods
359 [17].

360 Between-study variability is a main source of uncertainty for any meta-analysis and we
361 attempted to account for heterogeneity by using a random effects model when pooling prevalence
362 data and identify main sources of heterogeneity by subgroup and meta-regression analyses.
363 Nevertheless, there are other important limitations to our investigation that should be mentioned.
364 First, comparisons between CFDC-NS prevalence rates for different breakpoint criteria proposed by
365 CLSI, FDA, and EUCAST were partly indirect because not all studies reported susceptibility data using
366 all breakpoint definitions. Second, for a number of studies we inferred the susceptibility percentages

367 based on the maximum MICs being below the breakpoints. For example, in studies reporting
368 susceptibilities based on CLSI breakpoints (MIC \leq 4 mg /L) without reporting detailed MIC distribution
369 data, the susceptibility proportions based on EUCAST breakpoints or FDA breakpoints were
370 estimable only when the maximum MIC was lower than or equal to the EUCAST or FDA breakpoint
371 respectively (i.e. 100% susceptible). Bias from this approach would most likely be towards
372 underestimating CFDC-NS prevalence. Third, data on cefiderocol susceptibility for specific CR
373 phenotypes (MBL, NDM) were limited, and reporting bias is possible. Finally, cefiderocol
374 susceptibility testing has limitations including poor reproducibility of broth microdilution and disk
375 diffusion for *A. baumannii*, difficulties in interpretation due to trailing in broth microdilution and
376 colonies within zones of inhibition in disk diffusion, and inoculum-dependent MIC [17]. In our
377 review, most (84%) studies used broth microdilution, but about half were considered at moderate or
378 high risk of bias for not clearly reporting interpretation of trailing in broth microdilution.
379 Nevertheless, such lack of reporting does not necessarily mean that interpretation of trailing was
380 inappropriate. Moreover, meta-regression analyses did not detect variation in CFDC-NS prevalence
381 according to risk of bias assessments in the condition measurement domain.

382 In conclusion, cefiderocol currently maintains a good level of activity against major Gram-
383 negative pathogens and CFDC-NS prevalence is low overall. However, CFDC-NS prevalence
384 proportions were alarmingly high in specific CR phenotypes circulating in some institutions or
385 regions. A high index of suspicion for CFDC-NS is required concerning MBL- (predominantly NDM-)
386 producing Enterobacterales and *A. baumannii*, NDM-producing *P. aeruginosa*, as well as CZA-
387 resistant Enterobacterales, due to the possibility of emergence and spread of isolates with β -
388 lactamases that may significantly increase cefiderocol's MIC. Antimicrobial stewardship, infection
389 control and continued surveillance at the local level, as well as regular updating and reporting of
390 global CFDC-NS estimates, are imperative for preventing or delaying emerging resistance against
391 cefiderocol. Harmonization of EUCAST and CLSI breakpoints would help such efforts.

392

393 **Transparency declaration**

394

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404

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810 **TABLES**

811

812 **Table 1. Univariate meta-regression analysis of the associations between study-level characteristics and prevalence of cefiderocol non-susceptible**813 **carbapenem-resistant Enterobacterales based on CLSI breakpoints.**

814

Study characteristic	Level	S	Predicted CFDC-NS % (CI)	Odds ratio (CI)	P value	R ²
Year	2015-2019	5	5.4 (0.0 - 16.3)	Ref.	0.718	0.9%
	2020-2023	31	3.6 (0.5 - 6.7)	0.66 (0.07 - 6.46)		
Region ¹	EUR	12	3.1 (0.0 - 7.2)	0.72 (0.13 - 3.88)	0.700	6.8%
	AMR	8	1.1 (0.0 - 3.3)	0.21 (0.03 - 1.63)	0.136	
	WPR	6	9.6 (0.0 - 26.2)	3.27 (0.40 - 27.02)	0.272	
	Multi-regional	10	6.1 (0.0 - 15.1)	2.05 (0.33 - 12.64)	0.440	
Multinational	No	30	4.1 (0.5 - 7.7)	Ref.	0.662	1.5%
	Yes	6	2.6 (0.0 - 7.7)	0.61 (0.07 - 5.59)		
Multicenter	No	8	27.9 (0.0 - 57.9)	Ref.	0.001	28.1%
	Yes	28	2.2 (0.3 - 4.1)	0.06 (0.01 - 0.33)		

RoB, population and setting	Moderate/High risk	33	4.3 (0.7 - 7.8)	Ref.	0.337	3.1%
	Low risk	3	1.1 (0.0 - 4.1)	0.25 (0.01 - 4.23)		
RoB, condition measurement	Moderate/High risk	19	3.8 (0.0 - 7.9)	Ref.	0.992	0.0%
	Low risk	17	3.8 (0.0 - 8.2)	1.01 (0.20 - 5.06)		

815

816 S, the number of independent data sets in the analysis; CFDC-NS, Cefiderocol non-susceptible; CI, 95% confidence interval; EUR, European region; AMR,

817 Region of the Americas; WPR, Western Pacific Region; RoB, risk of bias.

818

819 ¹ Region defined by the WHO grouping. The odds ratio for each region compares that region to all other regions combined (e.g. EUR vs.. elsewhere).

820

821 **FIGURE CAPTIONS**

822

823 **Figure 2.** Summary forest plot of cefiderocol non-susceptibility against Enterobacterales

824 **S** is the number of independent sets of data in the analysis. **n / N** is the ratio of the cumulative number of isolates that were non-susceptible to cefiderocol
825 (**CFDC-NS**) over the total number of isolates, according to the respective definition of breakpoints and resistance phenotype. The centre of the diamond is
826 the population-averaged (pooled estimate) prevalence of CFDC-NS isolates. The length of the diamond indicates the 95% confidence interval (**CI**) for the
827 pooled estimate. The horizontal thick lines extending from the diamond represent the 95% prediction interval (**PI**) for the prevalence of CFDC-NS isolates
828 in new studies. **CAR**, carbapenem; **MBL**, metallo- β -lactamase; **NDM**, New Delhi metallo- β -lactamase; **CZA**, ceftazidime/avibactam; **CTA**,
829 ceftolozane/tazobactam

830

831 **Figure 3.** Summary forest plot of cefiderocol non-susceptibility against *P. aeruginosa*

832 **S** is the number of independent sets of data in the analysis. **n / N** is the ratio of the cumulative number of isolates that were non-susceptible to Cefiderocol
833 (**CFDC-NS**) over the total number of isolates, according to the respective definition of breakpoints and resistance phenotype. The centre of the diamond is
834 the population-averaged (pooled estimate) prevalence of CFDC-NS isolates. The length of the diamond indicates the 95% confidence interval (**CI**) for the
835 pooled estimate. The horizontal thick lines extending from the diamond represent the 95% prediction interval (**PI**) for the prevalence of CFDC-NS isolates

836 in new studies. **CAR**, carbapenem; **MBL**, metallo- β -lactamase; **NDM**, New Delhi metallo- β -lactamase; **CZA**, ceftazidime/avibactam; **CTA**,
837 ceftolozane/tazobactam

838

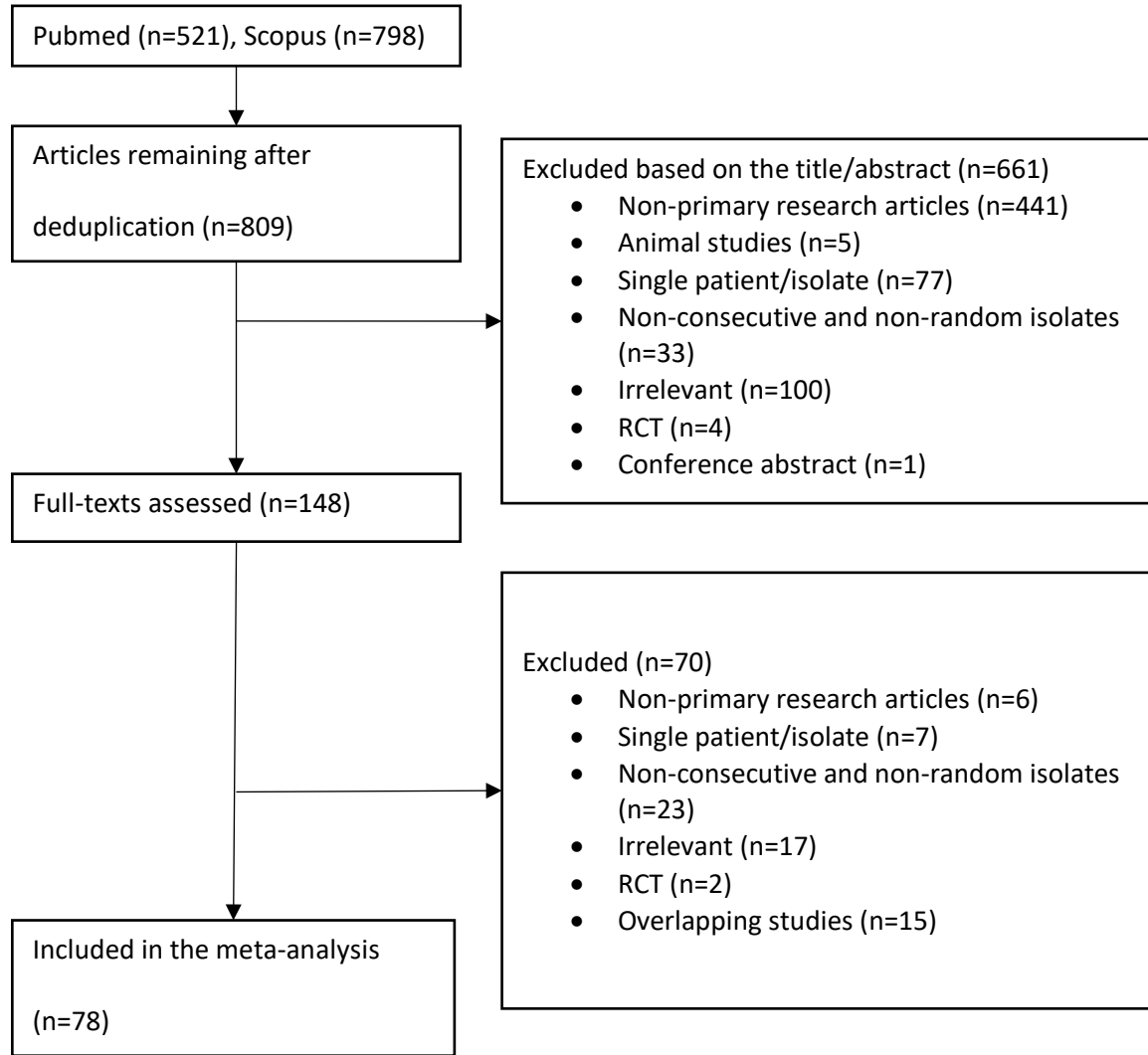
839 **Figure 4.** Summary forest plot of cefiderocol non-susceptibility against *A. baumannii*

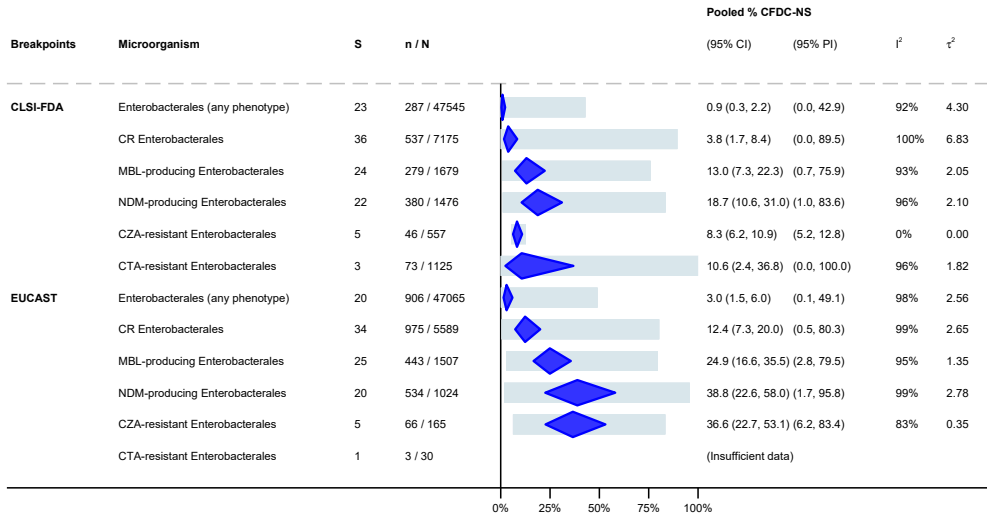
840 **S** is the number of independent sets of data in the analysis. **n / N** is the ratio of the cumulative number of isolates that were non-susceptible to Cefiderocol
841 (**CFDC-NS**) over the total number of isolates, according to the respective definition of breakpoints and resistance phenotype. The centre of the diamond is
842 the population-averaged (pooled estimate) prevalence of CFDC-NS isolates. The length of the diamond indicates the 95% confidence interval (**CI**) for the
843 pooled estimate. The horizontal thick lines extending from the diamond represent the 95% prediction interval (**PI**) for the prevalence of CFDC-NS isolates

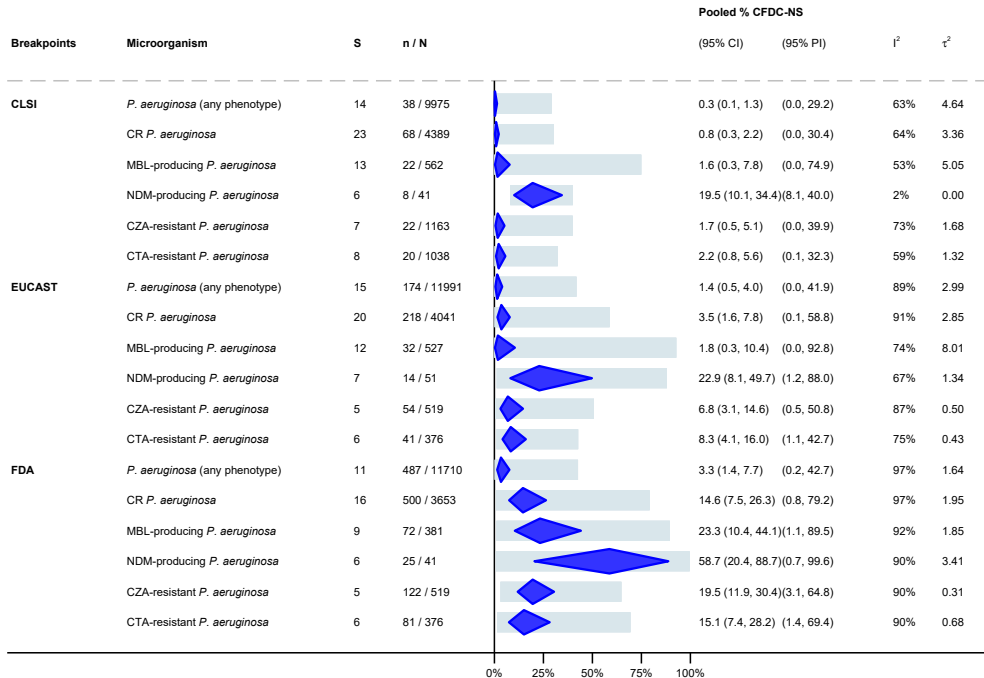
844 in new studies. **CAR**, carbapenem; **MBL**, metallo- β -lactamase; **NDM**, New Delhi metallo- β -lactamase; **CZA**, ceftazidime/avibactam; **CTA**,
845 ceftolozane/tazobactam

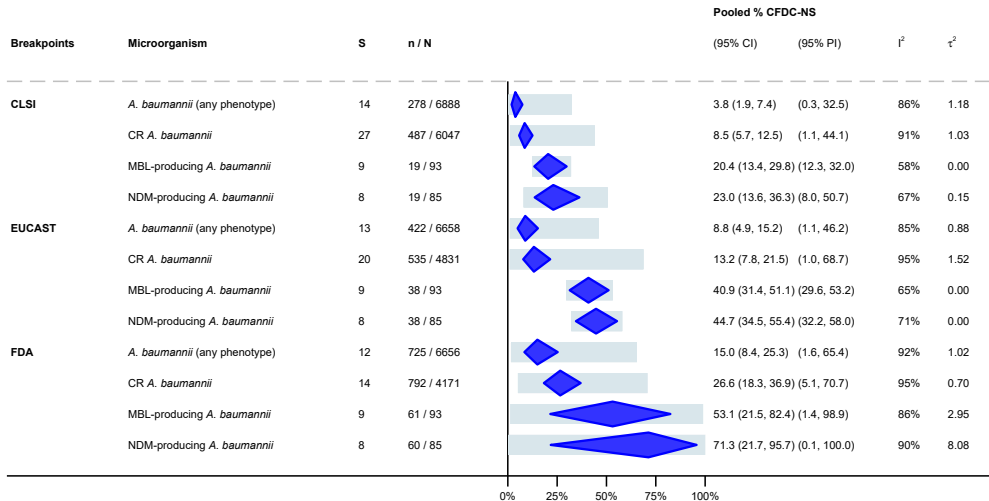
846

847 **Figure 1. Flow chart of the review**









Supplementary material

Global prevalence of cefiderocol non-susceptibility in Enterobacterales, *P. aeruginosa*, *A. baumannii* and *S. maltophilia*: a systematic review and meta-analysis

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Abbreviations

EUCAST	European Committee on Antimicrobial Susceptibility Testing
CAR	carbapenem
CLSI	Clinical and Laboratory Standards Institute
CTA	ceftolozane/tazobactam
CZA	ceftazidime/avibactam
MBL	metallo- β lactamase
NDM	New Delhi metallo- β lactamase,

1 Breakpoints for cefiderocol by FDA, CLSI and EUCAST

	FDA [1]				CLSI [2]				EUCAST [3]				
	MIC (mg/L)		Zone diameter in disk diffusion (mm)		MIC (mg/L)		Zone diameter in disk diffusion (mm)		MIC (mg/L)		Zone diameter in disk diffusion (mm)		
	S ≤	R >	S ≥	R <	S ≤	R >	S ≥	R <	S ≤	R >	S ≥	R <	ATU
Enterobacterales	4	8*	16	9*	4	8*	16	12*	2	2	22	22	18-22
<i>P. aeruginosa</i>	1	2*	22	13*	4	8*	18	13*	2	2	22	22	14-22
<i>A. baumannii</i>	1	2*	19	11*	4	8*	15	11*	2 [#]	2 [#]	17 [#]	ND [#]	ND
<i>S. maltophilia</i>	ND	ND	ND	ND	1	1 [§]	17	13*	2 [#]	2 [#]	20 [#]	ND [#]	ND

Abbreviations: **ATU**= area of technical uncertainty, **ND**= not defined, **R**= resistant, **S**= susceptible

* MICs or diameters between the S and R breakpoints are defined as intermediate.

Not species related PK/PD breakpoints proposed by EUCAST [3] and disk correlates [4]

§ CLSI susceptibility breakpoint for *S. maltophilia* have been recently modified to ≤1 mg/L.

In studies reporting only one set of criteria susceptibility percentages for other breakpoint criteria were inferred based on MIC distribution data when available or reported MIC ranges (when maximum MIC was below the susceptibility breakpoint a 0% non-susceptibility was inferred). Below are 3 examples to further clarify this approach:

In the study of “Falagas ME, 2017”, the breakpoints were not defined. However, based on reported MIC ranges for *P. aeruginosa* (≤0.03–1), all *P. aeruginosa* isolates were susceptible to cefiderocol according to all three breakpoint cutoffs (CLSI, EUCAST, FDA). On the contrary, based on reported MIC ranges for *K. pneumoniae* (≤0.03–4) only susceptibility based on CLSI breakpoints (susceptible if MIC≤4mg/L) was estimable (0% non-susceptible), while susceptibility based on EUCAST breakpoints (MIC≤2mg/L) could not be estimated (>0% to 10% non-susceptible based on max MIC 4mg/L and MIC₉₀ 1mg/L). In the study “Wang Y 2022” cefiderocol susceptibility was evaluated based on CLSI breakpoints (susceptible if MIC≤4mg/L). Nevertheless, MIC ranges were also reported. For example, cefiderocol’s MIC range against CR *K. pneumoniae* was <0.03 to 2mg/L. Therefore, all CR *K. pneumoniae* isolates were also susceptible by EUCAST breakpoints (MIC≤2mg/L). On the contrary, in the study “Jacobs MR, 2018”, also applying CLSI breakpoints, the MIC range for Enterobacterales was ≤0.03 to >64mg/L and detailed MIC distribution data

were not available. Therefore, susceptibility proportion based on EUCAST breakpoints was not estimable in this study (but >10% based on MIC90 4mg/L). In other words, in studies using CLSI breakpoints and not reporting detailed MIC distribution data, cefiderocol susceptibility proportion based on EUCAST breakpoints was estimable only when 100%.

2 Tool for risk of bias assessment

Domains/items assessed	Risk of bias assessment
Domain 1: Population and setting	Low risk of bias: Answer is “Yes” to at least 3 of 4 items Moderate/high risk of bias: Answer is “No” or “Unclear” to 2 or more items
○ Were study participants sampled in an appropriate way?	Yes: Inclusion of all consecutive isolates (as eligible per study inclusion criteria) or random sample of all consecutive isolates, and exclusion of duplicates (same pathogen isolated >1 time from the same patient) No: Convenience sampling or inclusion of duplicates Unclear: Above information not clearly reported
○ Was the sample size adequate?	Yes: Study has conducted a sample size calculation. If a sample size calculation was not provided a sample size was considered adequate if >1000 for each pathogen of interest (hypothesizing a prevalence of resistance of 1% ± 0.5%) No: Study does not report any sample size calculation and sample size (for each pathogen of interest) was less than 1000.
○ Were the study subjects and the setting described in detail?	Yes: Clear description of the characteristics of the study population, including patients’ age, setting (inpatients/outpatient/mixed), type of inpatients (ICU/non-IUC/mixed), antimicrobial resistance phenotype included (any/carbapenem-resistant/MDR/XDR/PDR), origin of the infection (healthcare-onset, community-onset) No: Any of the above information missing/ not clearly reported
○ Was the data analysis conducted with sufficient coverage of the identified sample?	Yes: No missing data on susceptibility to antimicrobials of interest or missing data unlikely to introduce coverage bias No: Missing data on susceptibility to antimicrobials of interest likely to introduce coverage bias (e.g. selective rather than universal susceptibility testing to antimicrobial of interest)
Domain 2: Condition measurement (susceptibility testing method) *	Low risk of bias: Answer is “Yes” to both items Moderate/high risk of bias: Answer is “No” or “Unclear” to either of the 2 items
○ Were valid methods used for the identification of the condition?	<ul style="list-style-type: none"> • <u>Yes:</u> BMD in iron-depleted cation-adjusted Mueller-Hinton broth or the Sensititer lyophilized BMD panel • <u>No:</u> Disk diffusion or gradient strip (acceptable, but less preferable methods [5])
○ Was the condition measured in a standard, reliable way for all participants?	<ul style="list-style-type: none"> • <u>Yes:</u> Clear definition of how trailing (BMD) or colonies within zone (disk diffusion) were interpreted (or appropriate citations of the correct method). • <u>No:</u> Lack of reporting of the above
Overall risk of bias assessment	Low risk: Study at low risk of bias in both domains Moderate/high risk: Study at moderate/high risk of bias in either domain

Tool adapted from the Joann-Briggs tool for quality assessment of prevalence studies [6, 7].

BMD= broth microdilution

* Studies referencing CLSI guidelines, EUCAST guidance [8] or prior publications describing the correct methodology for assessing susceptibility of cefiderocol [9-11] were considered at low risk of bias.

3 Characteristics of included studies

First author, publication year	Study type	Countries (number of institutions)	Period of isolate collection	Risk of bias assessment: <ul style="list-style-type: none"> Overall population and setting condition measurement 	Susceptibility data for;	Breakpoints used by the study, availability of MIC distribution data and definition of resistance phenotypes of included isolates
Alzayer M, 2023 [12] set 1	Surveillance study	Saudi Arabia (NA)	2015-2019	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> <i>K. pneumoniae</i> <i>E. coli</i> CR <i>K. pneumoniae</i> CR <i>E. coli</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI, MIC distributions available CR not defined. Isolates selected based on production of VIM/NDM/KPC or OXA-48-like
Alzayer M, 2023 [12] set 2	Surveillance study	Saudi Arabia (NA)	2018-2019	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> CR <i>A. baumannii</i> CR <i>P. aeruginosa</i> 	<ul style="list-style-type: none"> MIC distributions available CR not defined
Bakthavatchalam YD, 2023 [13]	Descriptive cohort	India (1)	2020-2022	<ul style="list-style-type: none"> Moderate/high Moderate/High Moderate/high 	<ul style="list-style-type: none"> NDM <i>E.coli</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI, MIC distribution available NDM <i>E.coli</i> co-harbours a PBP3 insert
Bianco G, 2023 [14]	Descriptive cohort	Italy (3)	2019-2022	<ul style="list-style-type: none"> Moderate/high Low risk Moderate/high 	<ul style="list-style-type: none"> CP Enterobacterales CR <i>P. aeruginosa</i> CR <i>A. baumannii</i> <i>S. maltophilia</i> 	<ul style="list-style-type: none"> Breakpoints: EUCAST
Cañada-García JE, 2023 [15]	Descriptive cohort	Spain (5)	2020-2021	<ul style="list-style-type: none"> Moderate/high Moderate/High Moderate/high 	<ul style="list-style-type: none"> CP <i>K. pneumoniae</i> 	<ul style="list-style-type: none"> Breakpoints: EUCAST

First author, publication year	Study type	Countries (number of institutions)	Period of isolate collection	Risk of bias assessment: <ul style="list-style-type: none"> Overall population and setting condition measurement 	Susceptibility data for;	Breakpoints used by the study, availability of MIC distribution data and definition of resistance phenotypes of included isolates
Galani I, 2023 [16]	Descriptive cohort	Greece (19)	2020-2021	<ul style="list-style-type: none"> Moderate/high Moderate/High Moderate/high 	<ul style="list-style-type: none"> CR <i>A. baumannii</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI, EUCAST. Distribution of inhibition zones available. 98.9% of isolates had MEM MIC\geq4 mg/L
Devoos L, 2023 [17]	Descriptive cohort	France (78)	2015-2022	<ul style="list-style-type: none"> Moderate/high Low risk Moderate/high 	<ul style="list-style-type: none"> MDR CR <i>P. aeruginosa</i> 	<ul style="list-style-type: none"> Breakpoints: EUCAST, MIC distribution available <i>P. aeruginosa</i> resistant to ceftazidime (MIC > 8 mg/L), imipenem (MIC > 4 mg/L) and ceftolozane/tazobactam (MIC > 4/4 mg/L)
Huang YS, 2023 [18]	Descriptive cohort	Taiwan (1)	2016-2021	<ul style="list-style-type: none"> Moderate/high Low risk Moderate/high 	<ul style="list-style-type: none"> MBL-producing CR Enterobacterales 	<ul style="list-style-type: none"> Breakpoints: CLSI. EUCAST non-susceptibility estimated based on Figure 1A. CR= MEM MIC\geq4 mg/L. Dual carbapenemase isolates excluded.
Ihssane B, 2023 [19]	Surveillance study	Morocco (NA)	2021	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> MBL <i>P. aeruginosa</i> 	<ul style="list-style-type: none"> Breakpoints: EUCAST (exact MICs reported) Isolates selected based on co-harboring NDM-VIM or VIM-IMP MBLs

First author, publication year	Study type	Countries (number of institutions)	Period of isolate collection	Risk of bias assessment: <ul style="list-style-type: none"> • Overall • population and setting • condition measurement 	Susceptibility data for;	Breakpoints used by the study, availability of MIC distribution data and definition of resistance phenotypes of included isolates
Kohira N, 2023 [20]	Surveillance study	China (5)	2020	<ul style="list-style-type: none"> • Moderate/high • Low risk • Moderate/high 	<ul style="list-style-type: none"> • Enterobacterales • <i>P. aeruginosa</i> • <i>A. baumannii</i> • <i>S. maltophilia</i> 	<ul style="list-style-type: none"> • Breakpoints: EUCAST + CLSI • CR= MEM non-susceptible based on CLSI
Lasarte-Monterrubio C, 2023 [21]	Descriptive cohort	Spain (NA)	NA	<ul style="list-style-type: none"> • Moderate/high • Moderate/high • Moderate/high 	<ul style="list-style-type: none"> • CP <i>E. cloacae</i> 	<ul style="list-style-type: none"> • Breakpoints: EUCAST, MIC distribution available
Le Terrier C, 2023 [22]	Surveillance	Switzerland (NA)	NA	<ul style="list-style-type: none"> • Moderate/high • Low risk • Moderate/high 	<ul style="list-style-type: none"> • MBL Enterobacterales • MBL <i>P. aeruginosa</i> 	<ul style="list-style-type: none"> • Breakpoints: EUCAST, MIC distribution available
Maraki S, 2023 [23]	Descriptive cohort	Greece (1)	2021	<ul style="list-style-type: none"> • Low risk • Low risk • Low risk 	<ul style="list-style-type: none"> • CP <i>K. pneumoniae</i> 	<ul style="list-style-type: none"> • Breakpoints: EUCAST • CR= CP <i>K. pneumoniae</i>. All were also resistant to IMI and MEM.
Marner M, 2023 [24]	Descriptive cohort	Germany (1)	2006-2018	<ul style="list-style-type: none"> • Moderate/high • Moderate/high • Moderate/high 	<ul style="list-style-type: none"> • MDR <i>P. aeruginosa</i> 	<ul style="list-style-type: none"> • Breakpoints: EUCAST. MIC distribution available. • MDR= resistant to the lead compounds of 3 or 4 of the following antibiotic classes: acyl ureidopenicillins (piperacillin or piperacillin-tazobactam), third- or

First author, publication year	Study type	Countries (number of institutions)	Period of isolate collection	Risk of bias assessment: <ul style="list-style-type: none"> • Overall • population and setting • condition measurement 	Susceptibility data for;	Breakpoints used by the study, availability of MIC distribution data and definition of resistance phenotypes of included isolates
						fourth-generation cephalosporins (ceftazidime and cefepime), fluoroquinolones (ciprofloxacin), and carbapenems (meropenem and imipenem)
Padovani M, 2023 [25]	Descriptive cohort	Italy (1)	2021-2022	<ul style="list-style-type: none"> • Moderate/high • Low risk • Moderate/high 	<ul style="list-style-type: none"> • Enterobacterales • <i>P. aeruginosa</i> • <i>A. baumannii</i> • <i>S. maltophilia</i> 	<ul style="list-style-type: none"> • Breakpoints: EUCAST
Pérez-Palacios P, 2023 [26]	Descriptive cohort	Morocco (1)	2019	<ul style="list-style-type: none"> • Low risk • Moderate/high • Moderate/high 	<ul style="list-style-type: none"> • MDR Enterobacterales (all <i>K. pneumoniae</i> or <i>E. hormaechei</i>) 	<ul style="list-style-type: none"> • Breakpoints: EUCAST. • MDR= “resistance to at least three families of antibiotics compared to the wild-type phenotype” • CR if MEM MIC>8mg/L
Potter RF, 2023 [27]	Descriptive cohort	USA (1)	2018-2020	<ul style="list-style-type: none"> • Moderate/high • Moderate/high • Moderate/high 	<ul style="list-style-type: none"> • Enterobacterales • <i>P. aeruginosa</i> • <i>A. baumannii</i> • <i>S. maltophilia</i> 	<ul style="list-style-type: none"> • Breakpoints: CLSI, EUCAST, FDA

First author, publication year	Study type	Countries (number of institutions)	Period of isolate collection	Risk of bias assessment: <ul style="list-style-type: none"> Overall population and setting condition measurement 	Susceptibility data for;	Breakpoints used by the study, availability of MIC distribution data and definition of resistance phenotypes of included isolates
Ruedas-López A, 2023 [28]	Descriptive cohort	Spain (1)	2020	<ul style="list-style-type: none"> Low risk Moderate/high Moderate/high 	<ul style="list-style-type: none"> CTA-resistant, CZA-resistant <i>P. aeruginosa</i> 	<ul style="list-style-type: none"> Breakpoints: MIC distribution available.
Sewunet T, 2023 [29]	Descriptive cohort	Ethiopia (1)	2016	<ul style="list-style-type: none"> Low risk Moderate/high Moderate/high 	<ul style="list-style-type: none"> CZA/MEM-resistant <i>P. aeruginosa</i> CR <i>A. baumannii</i> 	<ul style="list-style-type: none"> Breakpoints: EUCAST CR= MEM MIC>8mg/L
Tamma PD, 2023 [30]	Descriptive cohort	USA (3)	2016-2021	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> CR Enterobacterales 	<ul style="list-style-type: none"> Breakpoints: CLSI CR= resistant to at least 1 carbapenem or carrying at least 1 carbapenemase gene
Xu J, 2023 [31]	Descriptive cohort	China (1)	2016-2017	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> NDM CR <i>E. coli</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI, MIC distribution available
Badran SG, 2022 [32]	Descriptive cohort	Egypt (1)	2021	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> CR Enterobacterales MBL Enterobacterales 	<ul style="list-style-type: none"> Breakpoints: CLSI (only resistance proportion reported, non-susceptibility data not available) CR defined as resistance (by disk diffusion) to any of MEM, IMP, DOR, ETP
Ballesté-Delpierre C, 2022 [33]	Surveillance study	Argentina, Azerbaijan,	NA	<ul style="list-style-type: none"> Moderate/high Moderate/high 	<ul style="list-style-type: none"> <i>A. baumannii</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI, MIC distribution available

First author, publication year	Study type	Countries (number of institutions)	Period of isolate collection	Risk of bias assessment: <ul style="list-style-type: none"> Overall population and setting condition measurement 	Susceptibility data for;	Breakpoints used by the study, availability of MIC distribution data and definition of resistance phenotypes of included isolates
		Croatia, Greece, Italy, Morocco, Mozambique, Peru, Spain (NA)		<ul style="list-style-type: none"> Moderate/high 		<ul style="list-style-type: none"> CR defined as MEM MIC>8 mg/L
Bonnin RA, 2022 [5]	Descriptive cohort	France (NA)	2021	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> CR Enterobacterales 	<ul style="list-style-type: none"> Breakpoints: EUCAST, MIC distribution available CR= MEM>8mg/L
Cañada-García JE, 2022 [34]	Descriptive cohort	Spain (62)	2019-2019	<ul style="list-style-type: none"> Moderate/high Moderate/High Moderate/high 	<ul style="list-style-type: none"> CP <i>E. coli</i> and <i>K. pneumoniae</i> 	<ul style="list-style-type: none"> Breakpoints: EUCAST
Candel FJ, 2022 [35]	Surveillance study (SIDERO-WT*)	Europe (145)	2013-2018	<ul style="list-style-type: none"> Moderate/high Low risk Moderate/high 	<ul style="list-style-type: none"> Enterobacterales <i>P. aeruginosa</i> <i>A. baumannii</i> 	<ul style="list-style-type: none"> Breakpoints: EUCAST CR defined as MEM MIC>8 mg/L
Di Pilato V, 2022 [36]	Descriptive cohort	Italy (11)	2018-2019	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> NDM-1 producing <i>K. pneumoniae</i> 	<ul style="list-style-type: none"> Breakpoints: EUCAST, MIC distribution available
Daoud L, 2022[37]	Descriptive cohort	United Arab Emirates (3)	NA	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> <i>K. pneumoniae</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI, MIC distribution available CR= MEM MIC>8mg/L
Iovleva A, 2022 [38]	Descriptive cohort	USA (23)	2017-2018	<ul style="list-style-type: none"> Low risk Moderate/high Moderate/high 	<ul style="list-style-type: none"> CR <i>A. baumannii</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI CR= MEM or IMI MIC ≥4mg/L
Karlowsky JA, 2022 [39]	Surveillance study	USA, Canada, Europe (205)	2014-2019	<ul style="list-style-type: none"> Low risk Low risk 	<ul style="list-style-type: none"> Enterobacterales <i>P. aeruginosa</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI, MIC distribution available

First author, publication year	Study type	Countries (number of institutions)	Period of isolate collection	Risk of bias assessment: <ul style="list-style-type: none"> Overall population and setting condition measurement 	Susceptibility data for;	Breakpoints used by the study, availability of MIC distribution data and definition of resistance phenotypes of included isolates
	(SIDERO-WT*)			<ul style="list-style-type: none"> Low risk 	<ul style="list-style-type: none"> <i>A. baumannii</i> <i>S. maltophilia</i> 	<ul style="list-style-type: none"> MEM-nonsusceptible (MIC \geq 2 mg/L)
Karlowsky JA, 2022 [40]	Surveillance study (CANWARD)	Canada (NA)	2007	<ul style="list-style-type: none"> Moderate/high Low risk Moderate/high 	<ul style="list-style-type: none"> MDR/XDR <i>P. aeruginosa</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI, MIC distribution available MDR/XDR or not susceptible to any of the antipseudomonal agents tested. CR=meronem non-susceptible by CLSI 2022
Karpova EV, 2022 [41]	Descriptive cohort	Russia	2016-2021	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> XDR <i>K. pneumoniae</i> 	<ul style="list-style-type: none"> Breakpoints: EUCAST
Lan P, 2022 [42]	Descriptive cohort	China (15)	2018-2020	<ul style="list-style-type: none"> Low risk Low risk Low risk 	<ul style="list-style-type: none"> CR <i>K. pneumoniae</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI, MIC distribution available CR not defined
Lasarte-Monterrubio C, 2022 [43]	Descriptive cohort	Spain (3)	NA	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> CZA-R and CTA-R <i>P. aeruginosa</i> 	<ul style="list-style-type: none"> Breakpoints: EUCAST, MIC distribution available CZA-R and CTA-R <i>P. aeruginosa</i> following cephalosporin treatment

First author, publication year	Study type	Countries (number of institutions)	Period of isolate collection	Risk of bias assessment: <ul style="list-style-type: none"> Overall population and setting condition measurement 	Susceptibility data for;	Breakpoints used by the study, availability of MIC distribution data and definition of resistance phenotypes of included isolates
Mirza HC, 2022 [44]	Descriptive cohort	Turkey (1)	2014-2018	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> <i>CR P. aeruginosa</i> 	<ul style="list-style-type: none"> Breakpoints: EUCAST and CLSI CR= IMI-resistant by CLSI and EUCAST
Morroni G, 2022 [45]	Descriptive cohort	Italy (1)	2018-2019	<ul style="list-style-type: none"> Low risk Low risk Low risk 	<ul style="list-style-type: none"> CTA-R <i>P. aeruginosa</i> 	<ul style="list-style-type: none"> Breakpoints: EUCAST, MIC distribution available
Nayak G, 2022 [46]	Descriptive cohort	India (1)	2020-2021	<ul style="list-style-type: none"> Moderate/high Low risk Moderate/high 	<ul style="list-style-type: none"> CR Enterobacterales CR <i>P. aeruginosa</i> CR <i>A. baumannii</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI, MICI distribution available CR= resistance to any carbapenem (MEM, IMI, ETP, DOR)
Ramadan RA, 2022 [47]	Descriptive cohort	Egypt (1)	2020-2021	<ul style="list-style-type: none"> Low risk Moderate/high Moderate/high 	<ul style="list-style-type: none"> CR <i>K. pneumoniae</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI CR= non-susceptibility to at least one carbapenem (MEM, IMI, ETP, DOR)
Oueslati S, 2022 [48]	Surveillance study	France, Belgium (NA)	2012-2019	<ul style="list-style-type: none"> Moderate/high Low risk Moderate/high 	<ul style="list-style-type: none"> CR Enterobacterales CR <i>P. aeruginosa</i> CR <i>A. baumannii</i> <i>S. maltophilia</i> 	<ul style="list-style-type: none"> Breakpoints: EUCAST, MIC distribution available CR= carbapenemase-producing or CR by other mechanisms (but CR not-defined)

First author, publication year	Study type	Countries (number of institutions)	Period of isolate collection	Risk of bias assessment: <ul style="list-style-type: none"> Overall population and setting condition measurement 	Susceptibility data for;	Breakpoints used by the study, availability of MIC distribution data and definition of resistance phenotypes of included isolates
Shortridge D, 2022 [49]	Surveillance study (SENTRY)	Europe (35), USA (31)	2020	<ul style="list-style-type: none"> Moderate/high Low risk Moderate/high 	<ul style="list-style-type: none"> Enterobacterales <i>P. aeruginosa</i> <i>A. baumannii</i> <i>S. maltophilia</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI, EUCAST, FDA. CR defined as MEM/IMP MIC>2mg/L
Wang Q, 2022 [50]	Surveillance study (China CRE-Network)	China (48)	2018-2019	<ul style="list-style-type: none"> Moderate/high Low risk Moderate/high 	<ul style="list-style-type: none"> CR <i>E. coli</i> CR <i>K. pneumoniae</i> CR <i>Enterobacter cloacae</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI CR defined as resistance to at least 1 carbapenem or at least 1 carbapenemase production
Wang Y, 2022 [51]	Descriptive cohort	China (4)	2012-2018	<ul style="list-style-type: none"> Low risk Low risk Low risk 	<ul style="list-style-type: none"> CR <i>K. pneumoniae</i> CR <i>P. aeruginosa</i> CR <i>A. baumannii</i> <i>S. maltophilia</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI All isolates had MEM and IMP MIC ≥8mg/L
Weber C, 2022 [52]	Descriptive cohort	Germany (1)	2013-2017	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> CR <i>P. aeruginosa</i> 	<ul style="list-style-type: none"> Breakpoints: EUCAST CR= MDR nonsusceptible for at least piperacillin-tazobactam, ceftazidime, cefepime, imipenem, meropenem, and ciprofloxacin. Species
Zalas-Więcek P, 2022 [53]	Descriptive cohort	Poland (2)	2016-2022	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> MDR <i>E. coli</i> 	<ul style="list-style-type: none"> Breakpoints: EUCAST, MIC distribution available

First author, publication year	Study type	Countries (number of institutions)	Period of isolate collection	Risk of bias assessment: <ul style="list-style-type: none"> Overall population and setting condition measurement 	Susceptibility data for;	Breakpoints used by the study, availability of MIC distribution data and definition of resistance phenotypes of included isolates
Zhang Q, 2022 [54]	Descriptive cohort	USA (14)	2011-2018	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> CR Enterobacterales 	<ul style="list-style-type: none"> Breakpoints: CLSI, MIC distribution available CR defined as NS to at least 1 carbapenem (based on CLSI breakpoints)
Abdul-Mutakabbir JC, 2021 [55]	Surveillance study	USA (1)	NA	<ul style="list-style-type: none"> Moderate/high Low risk Moderate/high 	<ul style="list-style-type: none"> CR <i>A. baumannii</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI CR not defined (all isolates had MEM MIC >4mg/L)
Albano M, 2021 [56]	Surveillance studies	USA, Canada, Singapore (NA)	NA	<ul style="list-style-type: none"> Moderate/high Low risk Moderate/high 	<ul style="list-style-type: none"> Enterobacterales <i>P. aeruginosa</i> <i>A. baumannii</i> <i>S. maltophilia</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI, MIC distribution available Isolates selected for cefiderocol-resistance were excluded
Bhagwat SS, 2021 [57]	Surveillance study	Greece (15)	2014-2018	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> Enterobacterales <i>P. aeruginosa</i> <i>A. baumannii</i> 	<ul style="list-style-type: none"> Breakpoints: EUCAST, FDA CR defined as MEM MIC >8 mg/L and IMP MIC >4 mg/L
Carcione D, 2021 [58]	Surveillance study	Italy (1)	2020-2021	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> CR <i>A. baumannii</i> 	<ul style="list-style-type: none"> Breakpoints: EUCAST, MIC distribution available 17 of 20 isolates had MEM MIC >8mg/ml. Included only in the

First author, publication year	Study type	Countries (number of institutions)	Period of isolate collection	Risk of bias assessment: <ul style="list-style-type: none"> • Overall • population and setting • condition measurement 	Susceptibility data for;	Breakpoints used by the study, availability of MIC distribution data and definition of resistance phenotypes of included isolates
						CR/CNS/CP subgroup meta-analysis
Choby JE, 2021 [59]	Surveillance study (Georgia EIP)	USA (NA)	Different ranges per pathogen	<ul style="list-style-type: none"> • Moderate/high • Moderate/high • Moderate high 	<ul style="list-style-type: none"> • CR <i>Klebsiella</i> spp (2011-2015) • CR <i>P. aeruginosa</i> (2015-2016) • CR <i>A. baumannii</i> (2012-2015) • <i>S. maltophilia</i> (2018-2021) 	<ul style="list-style-type: none"> • Breakpoints: CLSI • CR not defined
Ghebremedhin B, 2021 [60]	Surveillance studies	Germany (1)	2014-2021	<ul style="list-style-type: none"> • Moderate/high • Moderate/high • Moderate/high 	<ul style="list-style-type: none"> • CR Enterobacterales • CR <i>P. aeruginosa</i> • CR <i>A. baumannii</i> 	<ul style="list-style-type: none"> • Breakpoints: EUCAST, MIC distribution available • CR not defined
Jacob A, 2021 [61]	Descriptive cohort	Belgium (1)	2015-2020	<ul style="list-style-type: none"> • Moderate/high • Moderate/high • Moderate/high 	<ul style="list-style-type: none"> • Enterobacterales 	<ul style="list-style-type: none"> • Breakpoints: EUCAST, CLSI, FDA • Selected for OXA-427 production
Johnston BD, 2021, [62]	Descriptive cohort	USA (1)	2012-2017	<ul style="list-style-type: none"> • Moderate/high • Moderate/high • Moderate/high 	<ul style="list-style-type: none"> • ESBL <i>E. coli</i> 	<ul style="list-style-type: none"> • Breakpoints: EUCAST, MIC distribution data available
Lee YL, 2021 [63]	Surveillance (SMART)	Taiwan (16)	2017-2020	<ul style="list-style-type: none"> • Moderate/high • Low risk • Moderate/high 	<ul style="list-style-type: none"> • <i>E. coli</i> • <i>K. pneumoniae</i> 	<ul style="list-style-type: none"> • Breakpoints: CLSI, MIC distribution available • For the CR subgroup in the meta-analysis only

First author, publication year	Study type	Countries (number of institutions)	Period of isolate collection	Risk of bias assessment: <ul style="list-style-type: none"> • Overall • population and setting • condition measurement 	Susceptibility data for;	Breakpoints used by the study, availability of MIC distribution data and definition of resistance phenotypes of included isolates
						the CP isolates were considered
Liu PY, 2021 [64]	Surveillance study (SMART)	Taiwan (16)	2018-2020	<ul style="list-style-type: none"> • Moderate/high • Low • Moderate/high 	<ul style="list-style-type: none"> • CR <i>P. aeruginosa</i> • CR <i>A. baumannii</i> 	<ul style="list-style-type: none"> • Breakpoints: CLSI • IMP MIC >2 mg/dl
Morris CP, 2021 [4]	Descriptive cohort	USA (1)	2017	<ul style="list-style-type: none"> • Moderate/high • Low • Moderate/high 	<ul style="list-style-type: none"> • CR Enterobacterales • CR <i>P. aeruginosa</i> • CR <i>A. baumannii</i> • <i>S. maltophilia</i> 	<ul style="list-style-type: none"> • Breakpoints: CLSI, EUCAST • ETP MIC \geq 2mg/dl for Enterobacterales • MEM MIC \geq 8mg/dl for <i>P. aeruginosa</i> and <i>A. baumannii</i>.
Biagi M, 2020 [65]	Surveillance study (SENTRY)	Multinational (detailed data not available)	2017-2018	<ul style="list-style-type: none"> • Moderate/high • Low • Moderate/high 	<ul style="list-style-type: none"> • <i>S. maltophilia</i> 	<ul style="list-style-type: none"> • Breakpoints: CLSI
Delgado-Valverde, 2020 [66]	Surveillance (PIRASOA programme)	Spain (27)	2014-2018	<ul style="list-style-type: none"> • Moderate/high • Low • Moderate/high 	<ul style="list-style-type: none"> • CP <i>K. pneumoniae</i> • CP <i>E. cloacae</i> • CP <i>P. aeruginosa</i> • CP-<i>A. baumannii</i> • <i>S. maltophilia</i> 	<ul style="list-style-type: none"> • Breakpoints: CLSI • ESBL and/or CP isolates selected. 112 of 125 Enterobacterales, all <i>A. baumannii</i> and all <i>P. aeruginosa</i> were CP
Golden RA, 2020 [67]	Surveillance study (CANWARD)	Canada (14)	2015-2017	<ul style="list-style-type: none"> • Moderate/high • Low risk • Moderate/high 	<ul style="list-style-type: none"> • Enterobacterales • <i>P. aeruginosa</i> • <i>A. baumannii</i> • <i>S. maltophilia</i> 	<ul style="list-style-type: none"> • Breakpoints: CLSI, MIC distribution available • CR Enterobacterales and <i>P. aeruginosa</i> defined based on

First author, publication year	Study type	Countries (number of institutions)	Period of isolate collection	Risk of bias assessment: <ul style="list-style-type: none"> • Overall • population and setting • condition measurement 	Susceptibility data for;	Breakpoints used by the study, availability of MIC distribution data and definition of resistance phenotypes of included isolates
						ertapenem- and meropenem non-susceptibility, respectively
Iregui A, 2020 [68], set 1	Surveillance study	USA (7)	2017	<ul style="list-style-type: none"> • Moderate/high • Low • Moderate/high 	<ul style="list-style-type: none"> • <i>E. coli</i> • <i>Enterobacter</i> spp • <i>K. pneumoniae</i> 	<ul style="list-style-type: none"> • Breakpoints: CLSI (“S” if MIC≤4mg/L)
Iregui A, 2020 [68], set 2	Surveillance study	USA (7)	2013-2014	<ul style="list-style-type: none"> • Moderate/high • Low • Moderate/high 	<ul style="list-style-type: none"> • CR <i>K. pneumoniae</i> • CR <i>P. aeruginosa</i> • CR <i>A. baumannii</i> 	<ul style="list-style-type: none"> • Breakpoints: CLSI (“S” if MIC≤4mg/L) • CR not defined
Iregui A, 2020 [68], set 3	Descriptive cohort	USA (NA)	NA	<ul style="list-style-type: none"> • Moderate/high • Low • Moderate/high 	<ul style="list-style-type: none"> • <i>K. pneumoniae</i> • <i>P. aeruginosa</i> • <i>A. baumannii</i> 	<ul style="list-style-type: none"> • Breakpoints: CLSI (“S” if MIC≤4mg/L). MIC distribution data available. • Isolates well-characterized for presence of b-lactamase and porin/efflux resistance mechanisms
Johnston BD, 2020 [69]	Surveillance study (MDH, SENTRY)	USA, China, India, Taiwan, Philippines, Thailand, Korea, Vietnam, Turkey,	MDH 2009-2017 SENTRY 2003-2017	<ul style="list-style-type: none"> • Moderate/high • Moderate/high • Moderate/high 	<ul style="list-style-type: none"> • CR <i>E. coli</i> 	<ul style="list-style-type: none"> • Breakpoints: EUCAST • “non-susceptible to ≥ 1 carbapenems” (CLSI M100-S27 cited)

First author, publication year	Study type	Countries (number of institutions)	Period of isolate collection	Risk of bias assessment: <ul style="list-style-type: none"> • Overall • population and setting • condition measurement 	Susceptibility data for;	Breakpoints used by the study, availability of MIC distribution data and definition of resistance phenotypes of included isolates
		Italy, Russia, Spain, UK, Israel, Belarus, Belgium, Germany, Greece, Poland, Chile, Argentina, Brazil, Mexico, Ecuador, Venezuela. (NA)				
Kresken M, 2020 [70], set 1	Surveillance study (Paul-Ehrlich society)	Germany (12)	2013-2014	<ul style="list-style-type: none"> • Low risk • Low risk • Low risk 	<ul style="list-style-type: none"> • Enterobacterales • <i>P. aeruginosa</i> • <i>A. baumannii</i> 	<ul style="list-style-type: none"> • Breakpoints: EUCAST, MIC distribution available
Kresken M, 2020 [70], set 2	Surveillance studies	Germany	2010-2017	<ul style="list-style-type: none"> • Moderate/high • Low risk • Moderate/high 	<ul style="list-style-type: none"> • CP Enterobacterales • CP <i>P. aeruginosa</i> • CP <i>A. baumannii</i> 	<ul style="list-style-type: none"> • Breakpoints: EUCAST, MIC distribution available • Isolates selected for carbapenemase production
Longshaw C, 2020 [71]	Surveillance study (SIDERO-CR)	Europe (110); predominantly Italy, Greece, Russia	2014-2016	<ul style="list-style-type: none"> • Moderate/high • Low risk • Moderate/high 	<ul style="list-style-type: none"> • CP Enterobacterales • CP <i>P. aeruginosa</i> • CP <i>A. baumannii</i> 	<ul style="list-style-type: none"> • Breakpoints: EUCAST, MIC distribution available • CR defined as MEM MIC ≥ 2mg/L. Overlap with Hackel MA, 2018 [72].

First author, publication year	Study type	Countries (number of institutions)	Period of isolate collection	Risk of bias assessment: <ul style="list-style-type: none"> • Overall • population and setting • condition measurement 	Susceptibility data for;	Breakpoints used by the study, availability of MIC distribution data and definition of resistance phenotypes of included isolates
						Useful for MBL data + for EUCAST breakpoints
Mushtaq S, 2020 [73]	Surveillance study (PHE-AMRHAI)	United Kingdom (NA)	2008-2018	<ul style="list-style-type: none"> • Moderate/high • Moderate/high • Moderate/high 	<ul style="list-style-type: none"> • CR Enterobacterales • CR <i>P. aeruginosa</i> • CR <i>A. baumannii</i> 	<ul style="list-style-type: none"> • Breakpoints: CLSI, FDA, EUCAST • CR not defined. Isolates selected based on carbapenemase production or CR associated with other mechanisms
Rolston KVI, 2020 [74]		USA (1)	2014-2017	<ul style="list-style-type: none"> • Moderate/high • Moderate/high • Moderate/high 	<ul style="list-style-type: none"> • Enterobacterales (including ESBL and CR subgroups) • MDR <i>P. aeruginosa</i> • <i>A. baumannii</i> • <i>S. maltophilia</i> 	<ul style="list-style-type: none"> • Breakpoints: CLSI (“S” if MIC≤4mg/L), MIC distribution data available • CR and MDR not defined
Talan DA, 2020 [75]	Descriptive cohort	USA (11)	2018-2019	<ul style="list-style-type: none"> • Low risk • Moderate/high • Moderate/high 	<ul style="list-style-type: none"> • Enterobacterales 	<ul style="list-style-type: none"> • Breakpoints: CLSI • ESBL
Trebosc V, 2020 [76]	Surveillance study (JMI laboratories)	Europe (144), USA (99), Asia-West Pacific (50)	2017-2019	<ul style="list-style-type: none"> • Moderate/high • Moderate/high • Moderate/high 	<ul style="list-style-type: none"> • CR <i>A. baumannii</i> 	<ul style="list-style-type: none"> • Breakpoints: CLSI • CR not defined (all isolates had MEM MIC>8mg/L)
Xie O, 2020 [77]	Descriptive cohort	Australia (1)	2015-2016	<ul style="list-style-type: none"> • Low risk • Moderate/high • Moderate/high 	<ul style="list-style-type: none"> • <i>E. coli</i> 	<ul style="list-style-type: none"> • Breakpoints: CLSI • ceftriaxone-non-susceptible

First author, publication year	Study type	Countries (number of institutions)	Period of isolate collection	Risk of bias assessment: <ul style="list-style-type: none"> Overall population and setting condition measurement 	Susceptibility data for;	Breakpoints used by the study, availability of MIC distribution data and definition of resistance phenotypes of included isolates
Hsueh SC, 2019 [78]	Descriptive cohort	Taiwan (1)	2016-2017	<ul style="list-style-type: none"> Moderate/high Low Moderate/high 	<ul style="list-style-type: none"> CR <i>P. aeruginosa</i> CR <i>A. baumannii</i> <i>S. maltophilia</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI ("S" if MIC≤4mg/L) IMP MIC ≥ 8mg/dl
Jacobs MR, 2018 [79]	Surveillance (ARGONAUT)	USA (NA)	NA	<ul style="list-style-type: none"> Moderate/high Low Moderate/high 	<ul style="list-style-type: none"> Enterobacteriales <i>P. aeruginosa</i> <i>A. baumannii</i> <i>S. maltophilia</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI ("S" if MIC≤4mg/L) Carbapenem-resistance defined as MEM MIC>1mg/L for Enterobacteriales, >2mg/L for <i>Acinetobacter</i> and <i>Pseudomonas</i>
Hackel MA, 2018 [72]	Surveillance study (IHMA)	24 countries in Europe, 10 countries in Latin America, 2 countries in North America, 8 countries in Asia, 3 countries in South Pacific, 2 countries in Africa, 3 countries in Middle East. (NA)	2014-2016	<ul style="list-style-type: none"> Moderate/high Low Moderate/high 	<ul style="list-style-type: none"> CR Enterobacteriales CR <i>P. aeruginosa</i> CR <i>A. baumannii</i> <i>S. maltophilia</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI ("S" if MIC≤4mg/L) MEM MIC ≥ 2mg/dl for Enterobacteriales MEM MIC ≥ 16 mg/dl for <i>P. aeruginosa</i> and <i>A. baumannii</i>.
Karlowsky JA, 2018 [10], set 1	Surveillance study	North America (45); USA, Canada	2015-2016	<ul style="list-style-type: none"> Moderate/high Low risk 	<ul style="list-style-type: none"> <i>Klebsiella</i> spp <i>E. coli</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI

First author, publication year	Study type	Countries (number of institutions)	Period of isolate collection	Risk of bias assessment: <ul style="list-style-type: none"> Overall population and setting condition measurement 	Susceptibility data for;	Breakpoints used by the study, availability of MIC distribution data and definition of resistance phenotypes of included isolates
	(SIDERO-WT*)			<ul style="list-style-type: none"> Moderate/high 	<ul style="list-style-type: none"> <i>Serratia</i> spp Enterobacter spp Citrobacter spp 	
Karlowsky JA, 2018 [10], set 2	Surveillance study (SIDERO-WT*)	Europe (55)	2015-2016	<ul style="list-style-type: none"> Moderate/high Low risk Moderate/high 	<ul style="list-style-type: none"> <i>Klebsiella</i> spp <i>E. coli</i> <i>Serratia</i> spp Enterobacter spp Citrobacter spp 	<ul style="list-style-type: none"> Breakpoints: CLSI
Kazmierczak KM 2018 [80]	Surveillance study (SIDERO-WT*)	Canada, United States, Czech Republic, France, Germany, Greece, Hungary, Italy, Russia, Spain, Sweden, Turkey, United Kingdom (99 hospitals total)	2014	<ul style="list-style-type: none"> Moderate/high Low Moderate/high 	<ul style="list-style-type: none"> MBL Enterobacterales MBL <i>P. aeruginosa</i> MBL <i>A. baumannii</i> 	<ul style="list-style-type: none"> Breakpoints: CLSI ("S" if MIC ≤ 4mg/L) Data extracted only for MBL producers*
Falagas ME, 2017 [81]	Descriptive cohort	Greece (18)	2010-2016	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> CR <i>K. pneumoniae</i> CR <i>E. cloacae</i> CR <i>P. stuartii</i> CR <i>P. aeruginosa</i> CR <i>A. baumannii</i> 	<ul style="list-style-type: none"> Breakpoints: not defined. MIC range, MIC₅₀ and MIC₉₀ reported. MEM MIC > 1mg/dl for Enterobacterales MEM MIC > 2mg/dl for <i>P. aeruginosa</i> and <i>A. baumannii</i>

First author, publication year	Study type	Countries (number of institutions)	Period of isolate collection	Risk of bias assessment: <ul style="list-style-type: none"> Overall population and setting condition measurement 	Susceptibility data for;	Breakpoints used by the study, availability of MIC distribution data and definition of resistance phenotypes of included isolates
Hackel MA, 2017 [11], set 1	Surveillance study (SIDERO-WT*)	North America (50); USA, Canada	2014-2015	<ul style="list-style-type: none"> Moderate/high Low risk Moderate/high 	<ul style="list-style-type: none"> Klebsiella spp E. coli Serratia spp Enterobacter spp Citrobacter spp 	<ul style="list-style-type: none"> Breakpoints: CLSI
Hackel MA, 2017 [11], set 2	Surveillance study (SIDERO-WT*)	Europe (49)	2014-2015	<ul style="list-style-type: none"> Moderate/high Low risk Moderate/high 	<ul style="list-style-type: none"> Klebsiella spp E. coli Serratia spp Enterobacter spp Citrobacter spp 	<ul style="list-style-type: none"> Breakpoints: CLSI
Kanazawa S, 2017 [82]	Surveillance study	Japan (1)	2010-2014	<ul style="list-style-type: none"> Moderate/high Low risk Moderate/high 	<ul style="list-style-type: none"> Enterobacterales 	<ul style="list-style-type: none"> Breakpoints: CLSI, MIC distribution available IMP-Susceptible (≤ 1mg/L) but MEM-Resistant (≥ 4mg/L) blaIMP-6
Ito A, 2016 [83], set 1	Descriptive cohort	Worldwide (NA)	2009-2011	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> <i>P. aeruginosa</i> <i>A. baumannii</i> <i>S. maltophilia</i> 	<ul style="list-style-type: none"> Breakpoints: Not defined. MIC distribution data available
Ito A, 2016 [83], set 2	Descriptive cohort	Worldwide (NA)	2000-2009	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> <i>P. aeruginosa</i> <i>A. baumannii</i> 	<ul style="list-style-type: none"> Breakpoints: Not defined. MIC distribution data available "β-lactam-resistant" isolates

First author, publication year	Study type	Countries (number of institutions)	Period of isolate collection	Risk of bias assessment: <ul style="list-style-type: none"> Overall population and setting condition measurement 	Susceptibility data for;	Breakpoints used by the study, availability of MIC distribution data and definition of resistance phenotypes of included isolates
Kohira N, 2016 [84], set 1	Surveillance study (IHMA)	North America, Europe, Africa, Asia, Latin America, South Pacific, Middle East (NA)	2009-2011	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> <i>E. coli</i> <i>K pneumoniae</i> <i>S marcescens</i> <i>C freundii</i> <i>E aerogenes</i> <i>E cloacae</i> 	<ul style="list-style-type: none"> Breakpoints: Not defined CR defined as meropenem MIC>4
Kohira N, 2016 [84], set 2	Surveillance study (JMI Laboratories)	North America, Europe, Asia-Pacific, and Latin America (NA)	2000-2009	<ul style="list-style-type: none"> Moderate/high Moderate/high Moderate/high 	<ul style="list-style-type: none"> <i>K pneumoniae</i> <i>S marcescens</i> <i>C freundii</i> <i>E cloacae</i> 	<ul style="list-style-type: none"> Breakpoints: Not defined, MIC distribution available Well-characterized for β-lactamases

Abbreviations: ARGONAUT= Antibacterial Resistance Leadership Group [ARLG] Reference Group for the testing of Novel Therapeutics, CP= carbapenemase-producing, CR= carbapenem-resistant (including carbapenem-nonsusceptible), DOR= doripenem EIP= Emerging Infections Program, ESBL= extended-spectrum β -lactamase, ETP= ertapenem, IHMA= International Health Management Associates, IMP= imipenem, MBL= metallo- β -lactamase producing, MDH= Minnesota Department of Health, MEM= meropenem, MIC= minimum inhibitory concentration, NA= not available, NS= non-susceptible, PHE-AMRHAI= Public Health England's Antimicrobial Resistance and Healthcare Associated Infections, PIRASOA= Institutional Programme for the Prevention and Control of Healthcare-Associated Infections and Appropriate Use of Antimicrobials (Andalusia), RCT= randomized controlled trial, SMART= Surveillance of Multicenter Antimicrobial Resistance in Taiwan

* See prior Table for data extracted from each SIDERO-WT publication

4 Summary table of study characteristics

Variable	Statistics ^{1,2}
Year of publication	
2015-2019	10 (13%)
2020-2023	68 (87%)
Region	
Europe	34 (40%)
Americas	18 (21%)
Western Pacific region	11 (13%)
Other region	10 (11%)
Multiple regions	13 (15%)
Multinational study	20 (24%)
Median number of countries (IQR)	1 (1-1)
Multicentre study	59 (69%)
Median number of hospitals (IQR)	4.5 (1-19)
Age group of patients	
Adults	5 (6%)
All ages	8 (9%)
Pediatric	1 (1%)
Not reported	72 (84%)
Type of patients	
Inpatients	12 (14%)
Outpatients	1 (1%)
Mixed	8 (9%)
Not reported	65 (76%)
Broth microdilution for CFDC susceptibility test	72 (84%)
MIC distribution reported	38 (44%)
Population and setting risk of bias	
Low	12 (14%)
Moderate-to-high	74 (86%)
Condition measurement risk of bias	
Low	40 (47%)
Moderate-to-high	46 (53%)
Overall risk of bias	
Low	5 (6%)
Moderate-to-high	81 (94%)

CFDC= cefiderocol

¹ Summary statistics are median (interquartile range) for continuous variables, and n (%) for categorical variables.

² 78 publications contributed 86 independent sets of data. Summary statistics for all variables, except the year of publication, were calculated over the 86 independent sets of data.

5 WHO regions

WHO-regions		Number of independent study sets*	%
Americas		28	33%
	Only in America	18	26%
	As part of multi-regional study	10**	12%
European region		43	50%
	Only in Europe	34	28%
	As part of multi-regional study	9**	11%
Western Pacific region		15	17%
	Only in Western Pacific region	11	13%
	As part of multi-regional study	4	5%
South-East Asia region		6	7%
	Only in South-East Asia region	2	2%
	As part of multi-regional study	4	5%
Africa		4	5%
	Only in Africa	1	1%
	As part of multi-regional study	3	4%
Eastern Mediterranean region		10	12%
	Only in Eastern Mediterranean region	7	8%
	As part of multi-regional study	3	4%
Not reported (multiple regions)		3	4%
Multiregional		13 **	15%

* n=78 studies contributing to n=86 independent data sets

**Including n=3 AMR, EUR, n=1 AMR, WPR, n=1 AMR, EUR, WPR, n=1 AMR, EUR, WPR, SEAR, n=1 AMR, EUR, EMR, AFR, n=1 AMR, UR, EMR, SEAR, n=1 AMR, EUR, EMR, SEAR, AFR, n=1 AMR, EUR, WPR, AFR, SEAR, n=3 multiple regions but regions not specified n=3

6 Critical appraisal of risk of bias of reviewed studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	PS	CM	Overall
Abdul-Mutakabbir JC, 2021	U	N	N	Y	Y	Y	MH	L	MH
Albano M (excl IHMA set), 2021	U	N	N	Y	Y	Y	MH	L	MH
Alzayer M, set 1, 2023	Y	N	N	Y	Y	N	MH	MH	MH
Alzayer M, set2, 2023	Y	N	N	Y	Y	N	MH	MH	MH
Badran SG, 2022	U	N	Y	Y	N	N	MH	MH	MH
Bakthavatchalam YD, 2023	U	N	N	Y	N	N	MH	MH	MH
Ballesté-Delpierre C, 2022	U	N	N	N	Y	N	MH	MH	MH
Bhagwat SS, 2021	Y	N	N	Y	Y	N	MH	MH	MH
Biagi M, 2020	U	N	N	Y	Y	Y	MH	L	MH
Bianco G, 2023	U	N	N	Y	Y	Y	MH	L	MH
Bonnin RA, 2022	U	N	N	Y	Y	N	MH	MH	MH
Candel FJ, 2022	Y	N	N	Y	Y	Y	MH	L	MH
Carcione D, 2021	U	N	N	Y	Y	N	MH	MH	MH
Cañada-García JE, 2022	Y	N	N	Y	N	N	MH	MH	MH
Cañada-García JE, 2023	Y	N	N	Y	N	N	MH	MH	MH
Choby JE, 2021	U	N	N	Y	N	Y	MH	MH	MH
Daoud L, 2022	U	N	N	Y	Y	N	MH	MH	MH
Delgado-Valverde M, 2020	U	N	N	Y	Y	Y	MH	L	MH
Devoos L, 2023	U	N	N	Y	Y	Y	MH	L	MH
Di Pilato V, 2022	N	N	Y	Y	N	N	MH	MH	MH
Falagas ME, 2017	Y	N	N	Y	Y	N	MH	MH	MH
Galani I, 2023	Y	N	N	Y	N	N	MH	MH	MH
Ghebremedhin B, 2021	U	N	N	Y	N	N	MH	MH	MH
Golden RA, 2020	U	N	N	Y	Y	Y	MH	L	MH
Hackel MA, 2018	U	N	N	Y	Y	Y	MH	L	MH
Hackel MA, Europe, 2017	U	N	N	Y	Y	Y	MH	L	MH
Hackel MA, North America, 2017	U	N	N	Y	Y	Y	MH	L	MH
Hsueh SC, 2019	U	N	N	Y	Y	Y	MH	L	MH
Huang YS, 2023	Y	N	N	Y	Y	Y	MH	L	MH
Ihssane B, 2023	U	N	N	Y	Y	N	MH	MH	MH
Iovleva A, 2022	Y	N	Y	Y	Y	N	L	MH	MH
Iregui A, set 1, 2020	U	N	N	Y	Y	Y	MH	L	MH
Iregui A, set 2, 2020	U	N	N	Y	Y	Y	MH	L	MH
Iregui A, set 3, 2020	N	N	N	Y	Y	Y	MH	L	MH
Ito A, set 1, 2015	Y	N	N	Y	N	N	MH	MH	MH
Ito A, set 2, 2015	Y	N	N	Y	N	N	MH	MH	MH
Jacob A, 2021	Y	N	N	Y	Y	N	MH	MH	MH
Jacobs MR, 2018	U	N	N	Y	Y	Y	MH	L	MH
Johnston BD, 2020	U	N	N	Y	Y	N	MH	MH	MH
Johnston BD, 2021	Y	N	N	Y	Y	N	MH	MH	MH
Kanazawa S, 2017	U	N	N	Y	Y	Y	MH	L	MH
Karlowisky JA (1), 2022	Y	N	N	Y	Y	Y	MH	L	MH
Karlowisky JA (2), 2022	Y	N	N	Y	Y	Y	MH	L	MH
Karlowisky JA, Europe, 2018	Y	N	N	Y	Y	Y	MH	L	MH
Karlowisky JA, North America, 2018	Y	N	N	Y	Y	Y	MH	L	MH
Karpova EV, 2022	U	N	N	Y	Y	N	MH	MH	MH
Kazmierczak KM, 2019	U	N	N	Y	Y	Y	MH	L	MH
Kohira N, 2023	U	N	N	Y	Y	Y	MH	L	MH
Kohira N, set 1, 2016	Y	N	N	Y	N	N	MH	MH	MH
Kohira N, set 2, 2016	U	N	N	Y	N	N	MH	MH	MH

Kresken M, set 1, 2020	Y	N	Y	Y	Y	Y	L	L	L
Kresken M, set 2, 2020	Y	N	N	Y	Y	Y	MH	L	MH
Lan P, 2022	Y	N	Y	Y	Y	Y	L	L	L
Lasarte-Monterrubio C, 2022	U	N	Y	Y	Y	N	MH	MH	MH
Lasarte-Monterrubio C, 2023	U	N	N	Y	Y	N	MH	MH	MH
Le Terrier C, 2023	U	N	N	Y	Y	Y	MH	L	MH
Lee YL, 2021	U	N	N	Y	Y	Y	MH	L	MH
Liu PY, 2021	U	N	N	Y	Y	Y	MH	L	MH
Longshaw C, 2020	U	N	N	Y	Y	Y	MH	L	MH
Maraki S, 2023	Y	N	Y	Y	Y	Y	L	L	L
Marner M, 2023	U	N	Y	Y	N	Y	MH	MH	MH
Morris CP, 2021	Y	N	N	Y	Y	Y	MH	L	MH
Morrioni G, 2022	Y	N	Y	Y	Y	Y	L	L	L
Mushtaq S, 2020	Y	N	N	Y	Y	N	MH	MH	MH
Mirza HC, 2022	Y	N	N	Y	N	N	MH	MH	MH
Nayak G, 2022	Y	N	N	Y	Y	Y	MH	L	MH
Oueslati S, 2022	U	N	N	Y	Y	Y	MH	L	MH
Ozyurt OK, 2023	U	N	N	Y	N	N	MH	MH	MH
Padovani M, 2023	Y	N	N	Y	Y	Y	MH	L	MH
Potter RF, 2023	U	N	N	Y	Y	N	MH	MH	MH
Pérez-Palacios P, 2023	Y	N	Y	Y	Y	N	L	MH	MH
Ramadan RA, 2022	Y	N	Y	Y	N	N	L	MH	MH
Rolston KVI, 2020	U	N	N	Y	Y	N	MH	MH	MH
Ruedas-López A, 2023	Y	N	Y	Y	Y	N	L	MH	MH
Sewunet T, 2023	Y	N	Y	Y	N	N	L	MH	MH
Shortridge D, 2022	Y	N	N	Y	Y	Y	MH	L	MH
Talan DA, 2020	Y	N	Y	Y	N	N	L	MH	MH
Tamma PD, 2023	Y	N	N	Y	Y	N	MH	MH	MH
Trebosc V, 2020	U	N	N	Y	Y	N	MH	MH	MH
Wang Q, 2022	U	N	N	Y	Y	Y	MH	L	MH
Wang Y, 2022	Y	N	Y	Y	Y	Y	L	L	L
Weber C, 2022	U	N	N	Y	N	N	MH	MH	MH
Xie O, 2020	Y	N	Y	Y	N	N	L	MH	MH
Xu J, 2023	Y	N	N	N	Y	N	MH	MH	MH
Zalas-Więcek P, 2022	U	N	N	Y	N	N	MH	MH	MH
Zhang Q, 2022	U	N	N	Y	Y	N	MH	MH	MH

Notes.

PS, population and setting domain; **CM**, condition measurement domain, **Y/U/N**, yes/unclear/no; **L**; low risk of bias; **MH**, moderate-to-high risk of bias.

Q1: Were study participants sampled in an appropriate way?

Q2: Was the sample size adequate?

Q3: Were the study subjects and the setting described in detail?

Q4: Was the data analysis conducted with sufficient coverage of the identified sample?

Q5: Were valid methods used for the identification of the condition?

Q6: Was the condition measured in a standard, reliable way for all participants?

7 Overview of SIDERO-WT publications

First author, publication year	Study period	Countries-isolates involved	Notes regarding overlap	Included/ excluded in the meta-analysis
Karlow sky, 2022 [39]	2014-2019	Total* all isolates	Overlap with all prior SIDERO-WT publications (but no separate data for different Enterobacterales spp)	Included
Candel FJ, 2022 [35]	2014-2019	Europe all isolates	Overlap with Karlow sky 2022 but additional data for each Enterobacterales spp and from SIDERO-Proteeae	Included in meta-analyses for specific Enterobacterales spp (EUCAST breakpoints)
Thelen P, 2022 [85]	2014-2018	Germany all isolates	Overlap with Karlow sky 2022, Candel 2022, Karlow sky 2018 and Hackel 2017	Excluded
Stracquadanio S, 2021 [86]	2014-2018	Italy all isolates	Overlap with Karlow sky 2022, Candel 2022, Karlow sky 2018 and Hackel 2017	Excluded
Cercenado E, 2021 [87]	2014-2018	Spain all isolates	Overlap with Karlow sky 2022, Candel 2022, Karlow sky 2018 and Hackel 2017	Excluded
Naas T, 2021 [88]	2014-2018	France all isolates	Overlap with Karlow sky 2022, Candel 2022, Karlow sky 2018 and Hackel 2017	Excluded
Gant V, 2021 [89]	2014-2018	England all isolates	Overlap with Karlow sky 2022, Candel 2022, Karlow sky 2018 and Hackel 2017	Excluded
Karlow sky et al 2018 [10]	2015-2016	Total* all isolates	Overlap with Karlow sky	Included in meta-analyses for specific Enterobacterales spp (CLSI breakpoints)
Sato T, 2020 [90]	2014	Total* E. coli isolates with four	Selection of isolates from SIDERO-WT 2014	Excluded

		aminoacid insertion in PBP-3		
Kohira et al 2020 [91]	2014	Total* isolates with cefiderocol MIC>4 mg/L	Subgroup of isolates from SIDERO-WT 2014	Excluded (no data of interest for meta-analysis)
Kazmierczak KM 2018 [80]	2014	Total* carbapenem NS isolates	Subgroup of isolates from SIDERO-WT 2014	Included for meta-analysis of MBL-producers subgroups.
Hackel MA, 2017 [11]	2014-2015	Total*- all isolates	Subgroups of isolates reported in Kazmierczak 2018 and Kohira 2020)	Included in meta-analyses for specific Enterobacterales spp (CLSI breakpoints)

Abbreviations: MIC= minimum inhibitory concentration, NS= non-susceptible

* USA, Canada, Europe (Austria, Belgium, Croatia, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Romania, Russia, Serbia, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom)

8 Meta-analysis of cefiderocol non-susceptibility in Enterobacterales

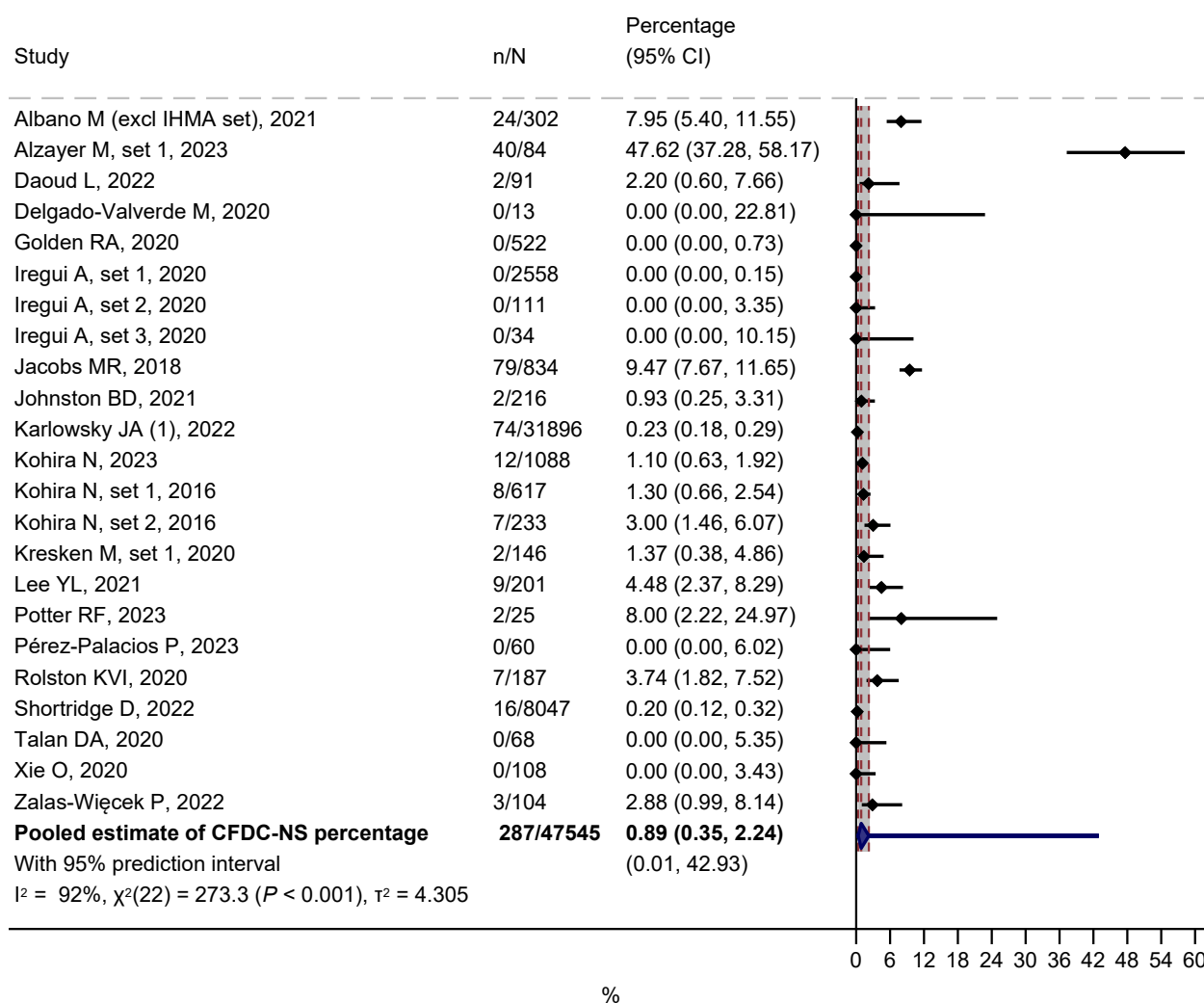
8.1 Summary table

Enterobacterales	Breakpoints	S	n/N	CFDC -NS %	Lower CL, %	Upper CL, %	I ² , %	τ ²	Lower PL, %	Upper PL, %
Any phenotype	CLSI-FDA	23	287/47545	0.9	0.3	2.2	92	4.305	0.0	42.9
	EUCAST	20	906/47065	3.0	1.5	6.0	98	2.561	0.1	49.1
CR	CLSI-FDA	36	537/7175	3.8	1.7	8.4	10	6.827	0.0	89.5
	EUCAST	34	975/5589	12.4	7.3	20.0	99	2.646	0.5	80.3
MBL-producing	CLSI-FDA	24	279/1679	13.0	7.3	22.3	93	2.047	0.7	75.9
	EUCAST	25	443/1507	24.9	16.6	35.5	95	1.347	2.8	79.5
NDM-producing	CLSI-FDA	22	380/1476	18.7	10.6	31.0	96	2.099	1.0	83.6
	EUCAST	20	534/1024	38.8	22.6	58.0	99	2.778	1.7	95.8
CZA-resistant	CLSI-FDA	5	46/557	8.3	6.2	10.9	0	0.000	5.2	12.8
	EUCAST	5	66/165	36.6	22.7	53.1	83	0.345	6.2	83.4
CTA-resistant	CLSI-FDA	3	73/1125	10.6	2.4	36.8	96	1.816	0.0	100.0
	EUCAST	1	3/30

S is the number of independent datasets in the analysis (a single study may have contributed more than one sets of data). n/N is the ratio of the cumulative number of Enterobacterales isolates that were non-susceptible to Cefiderocol (CFDC-NS) over the total number of isolates, according to the respective definition of breakpoints and resistance phenotype. CFDC-NS, cefiderocol non-susceptible; CL, 95% confidence limit; PL, 95% prediction limit; CAR, carbapenem; MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; CZA, ceftazidime/avibactam; CTA, ceftolozane/tazobactam

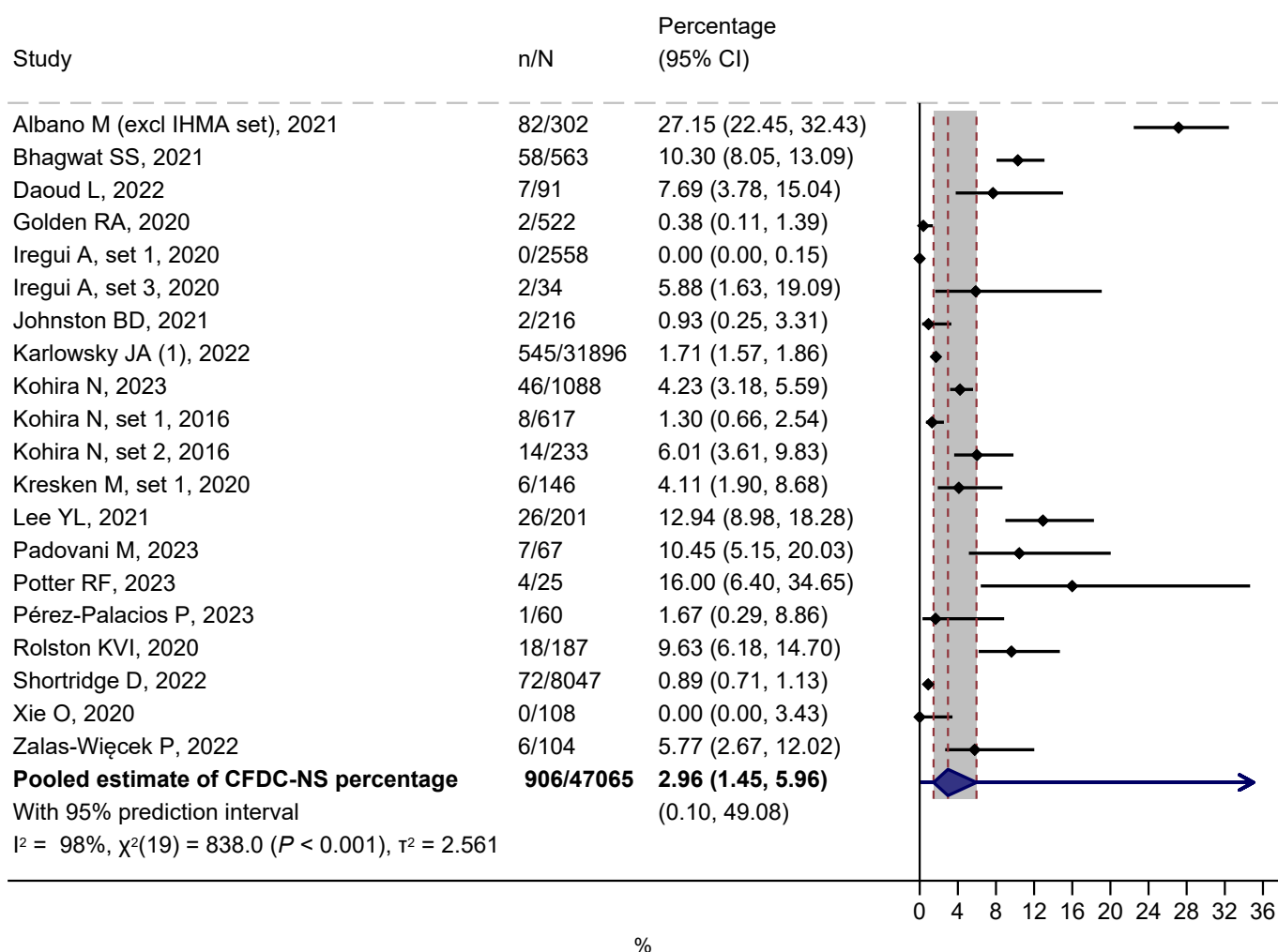
8.2 Forest plots

8.2.1 Enterobacterales, any phenotype; CLSI-FDA



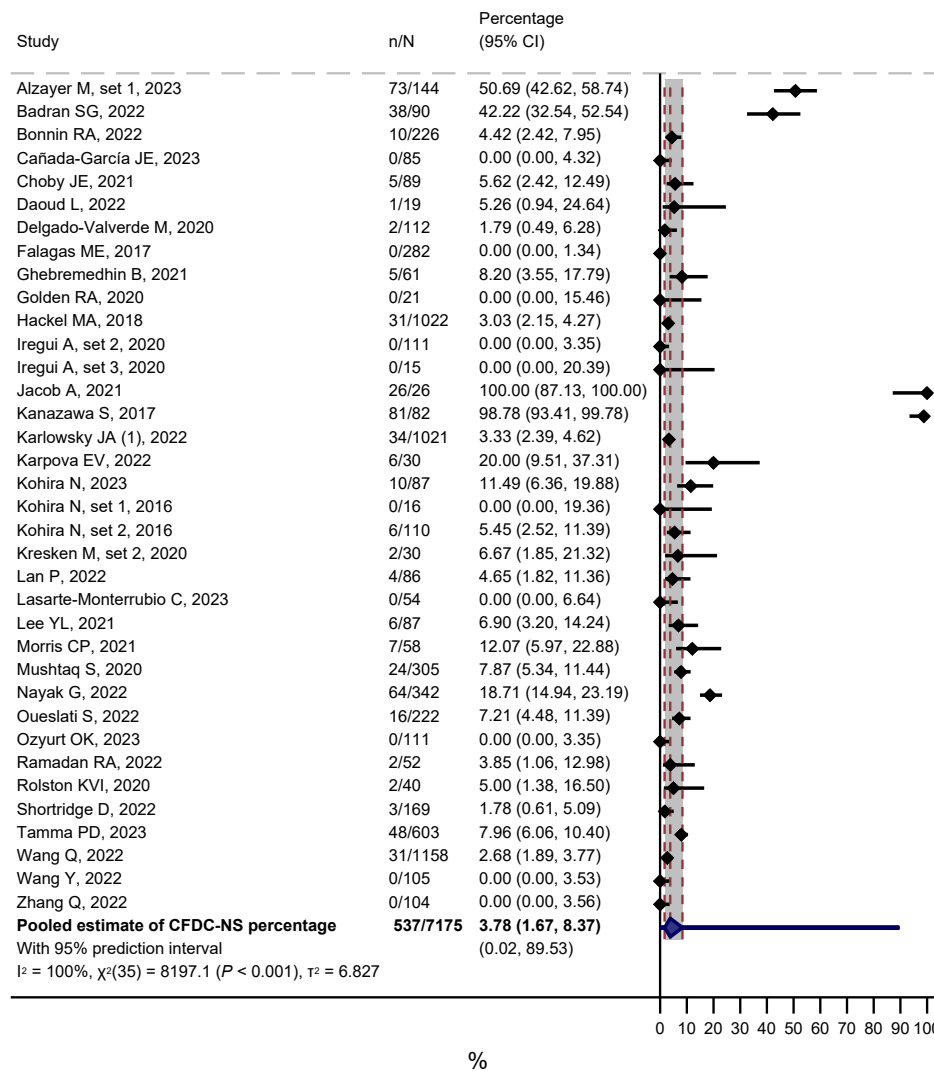
Note. n is the number of Enterobacterales (any phenotype) isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to CLSI-FDA breakpoints. N is the overall number of Enterobacterales (any phenotype) clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

8.2.2 Enterobacterales, any phenotype; EUCAST



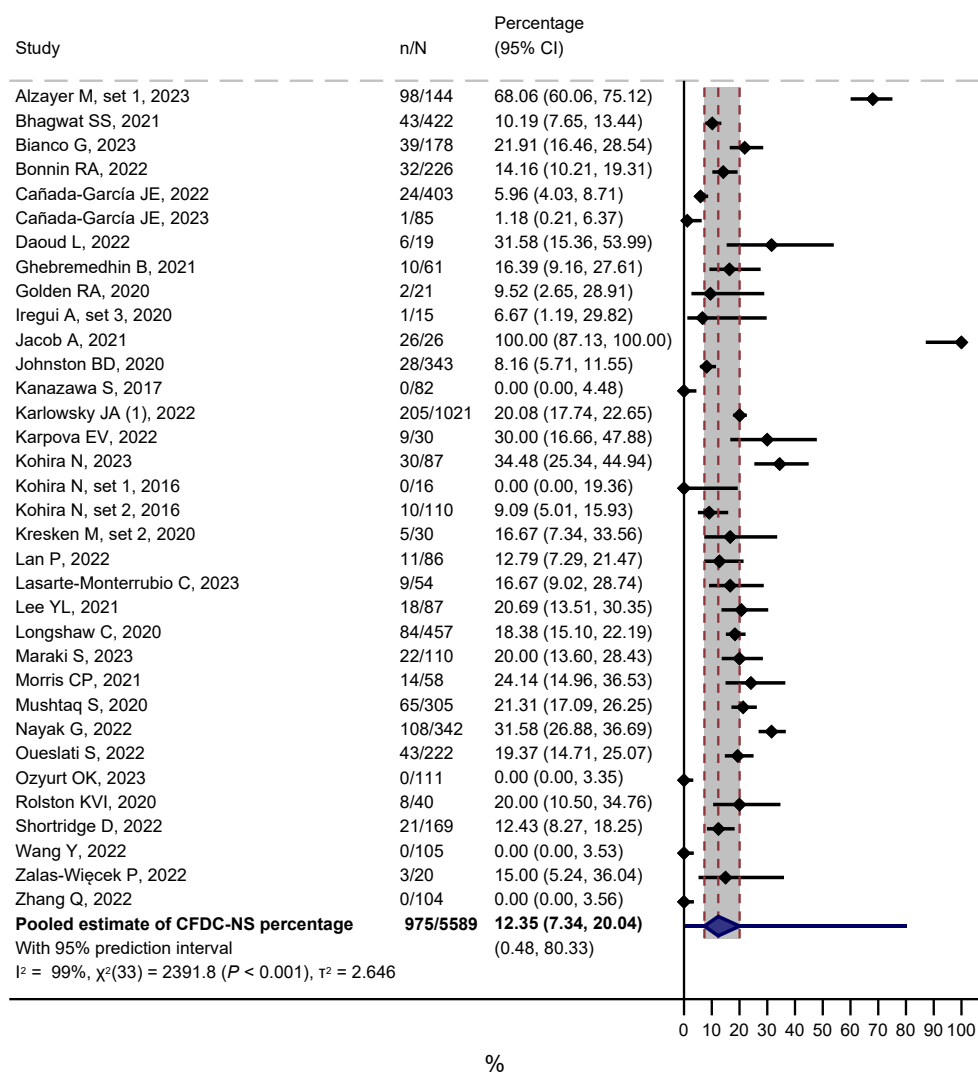
Note. n is the number of Enterobacterales (any phenotype) isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to EUCAST breakpoints. N is the overall number of Enterobacterales (any phenotype) clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

8.2.3 Enterobacterales, carbapenem-resistant; CLSI-FDA



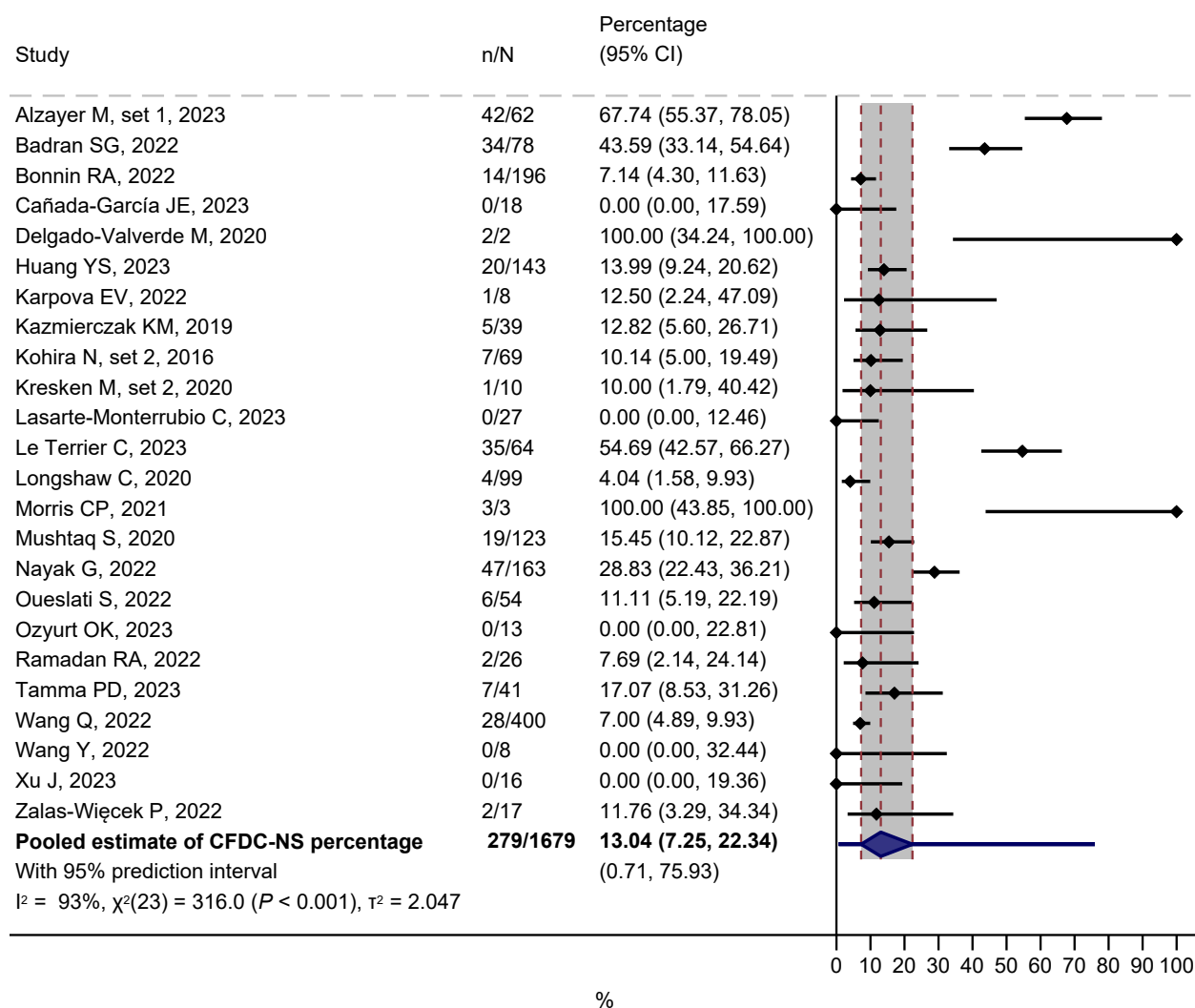
Note. n is the number of CR Enterobacterales isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to CLSI-FDA breakpoints. N is the overall number of CR Enterobacterales clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

8.2.4 Enterobacterales, carbapenem-resistant; EUCAST



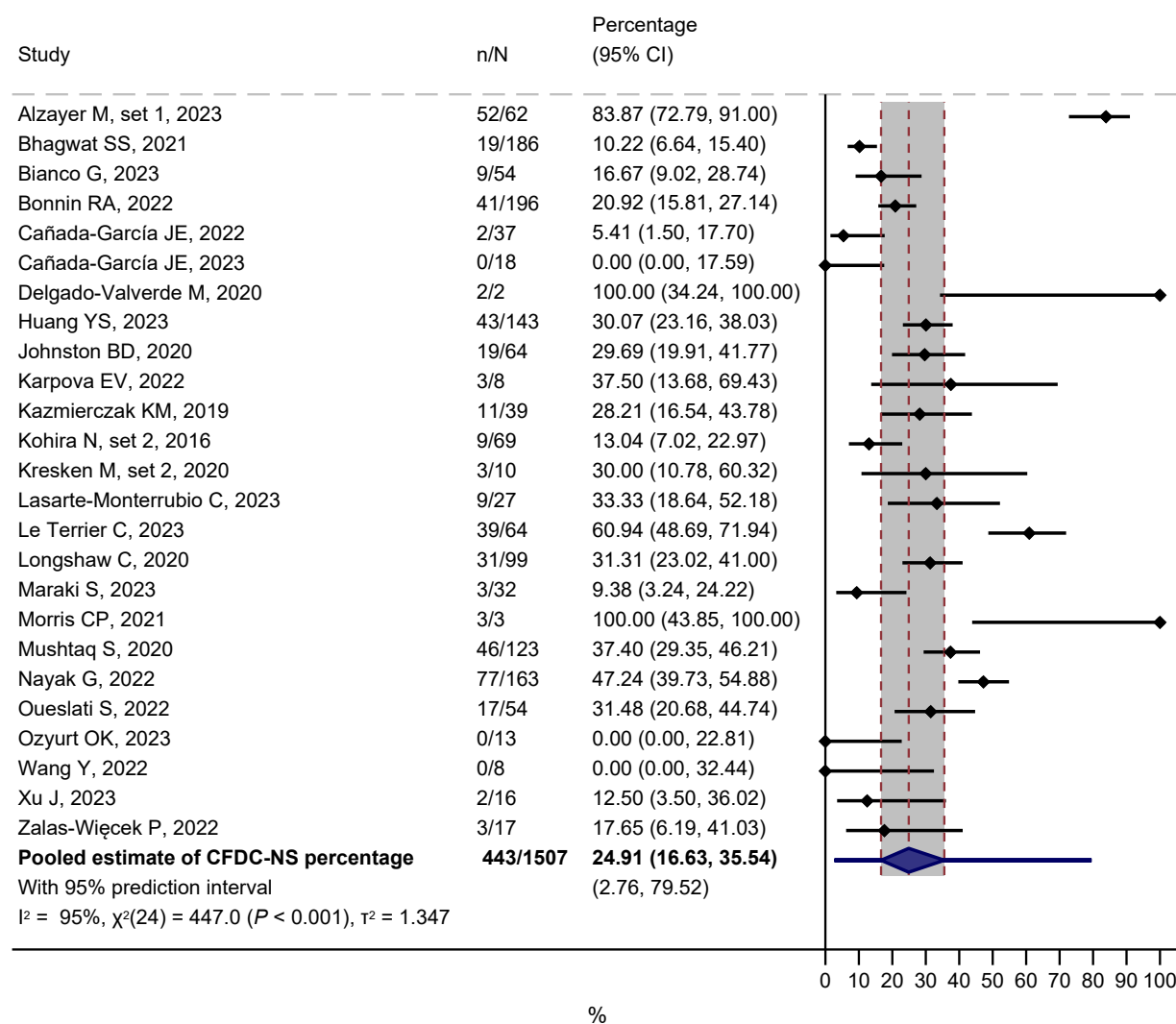
Note. n is the number of CR Enterobacterales isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to EUCAST breakpoints. N is the overall number of CR Enterobacterales clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

8.2.5 Enterobacterales, MBL-producing; CLSI-FDA



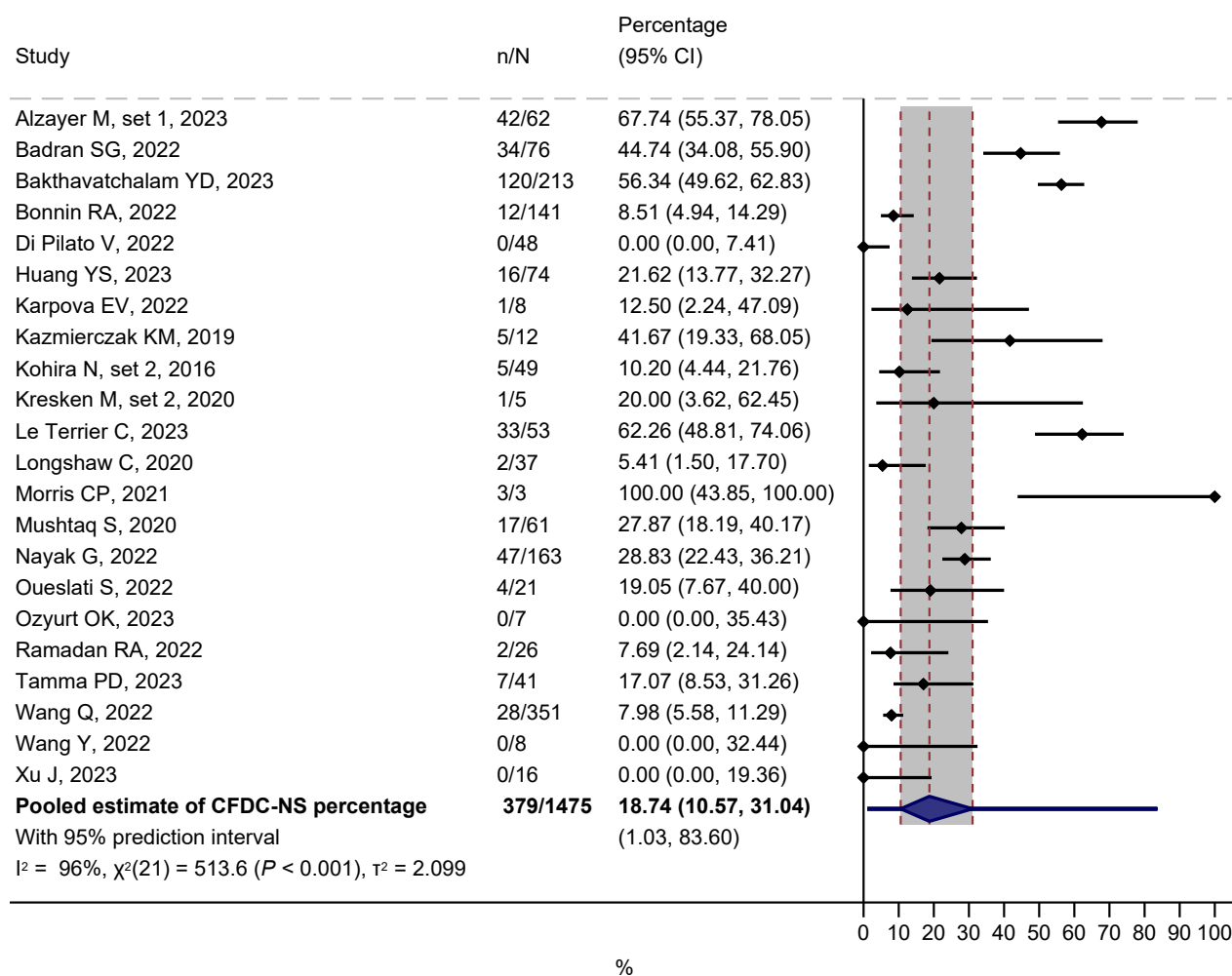
Note. n is the number of MBL-producing Enterobacterales isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to CLSI-FDA breakpoints. N is the overall number of MBL-producing Enterobacterales clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

8.2.6 Enterobacterales, MBL-producing; EUCAST



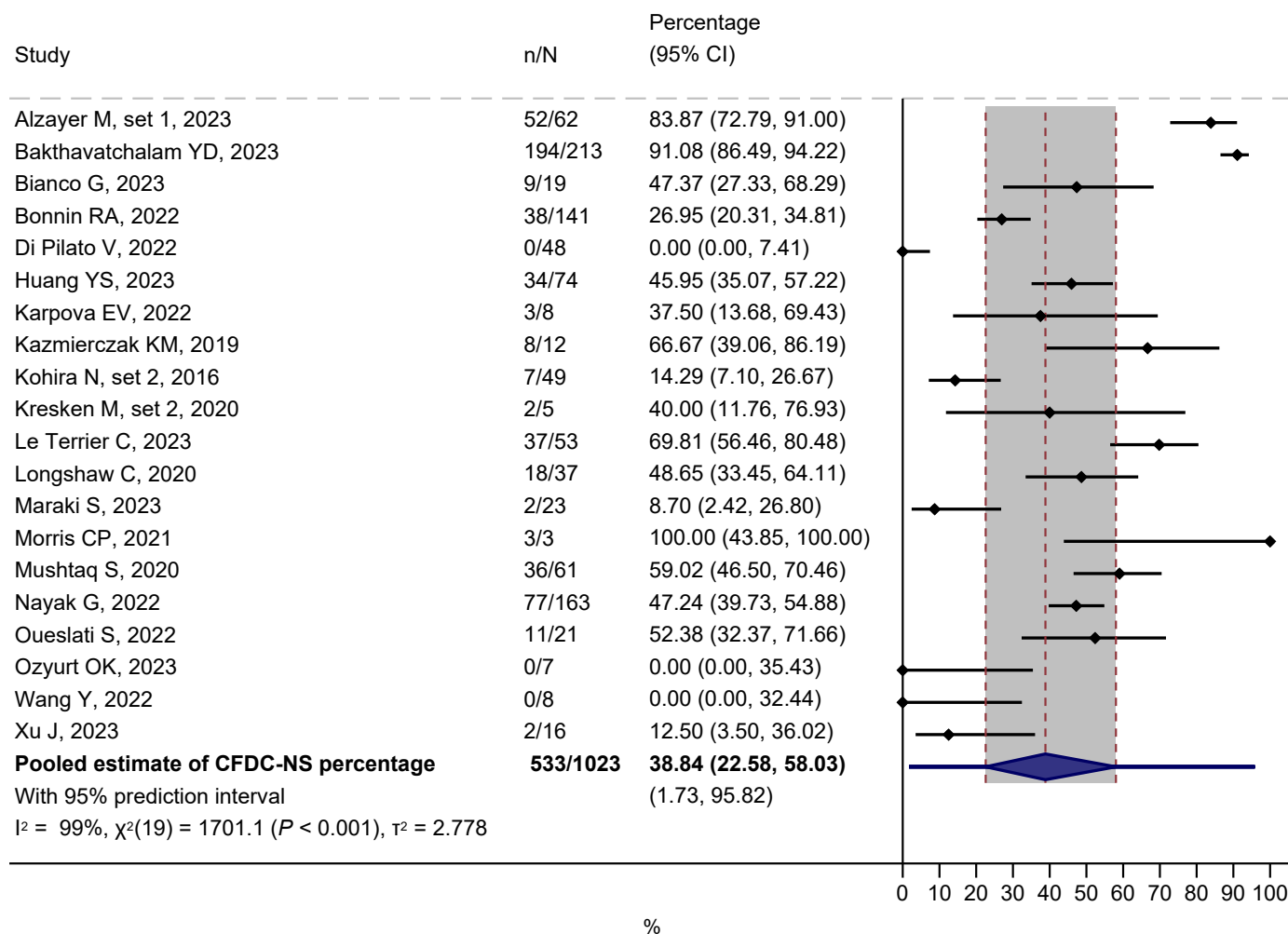
Note. n is the number of MBL-producing Enterobacterales isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to EUCAST breakpoints. N is the overall number of MBL-producing Enterobacterales clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

8.2.7 Enterobacterales, NDM-producing; CLSI-FDA



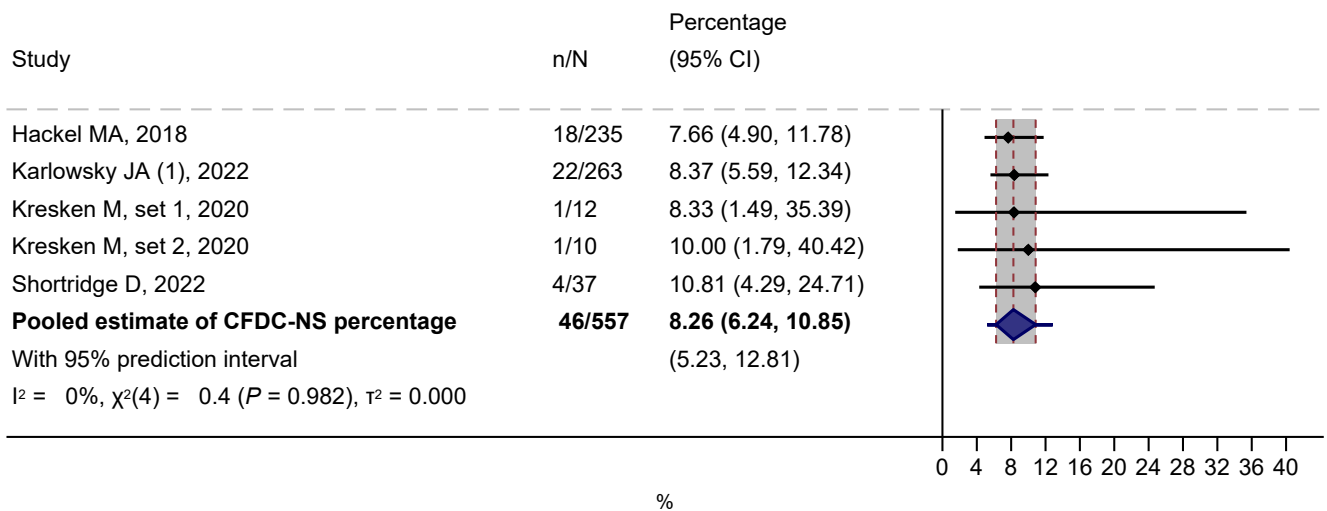
Note. n is the number of NDM-producing Enterobacterales isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to CLSI-FDA breakpoints. N is the overall number of NDM-producing Enterobacterales clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

8.2.8 Enterobacterales, NDM-producing; EUCAST



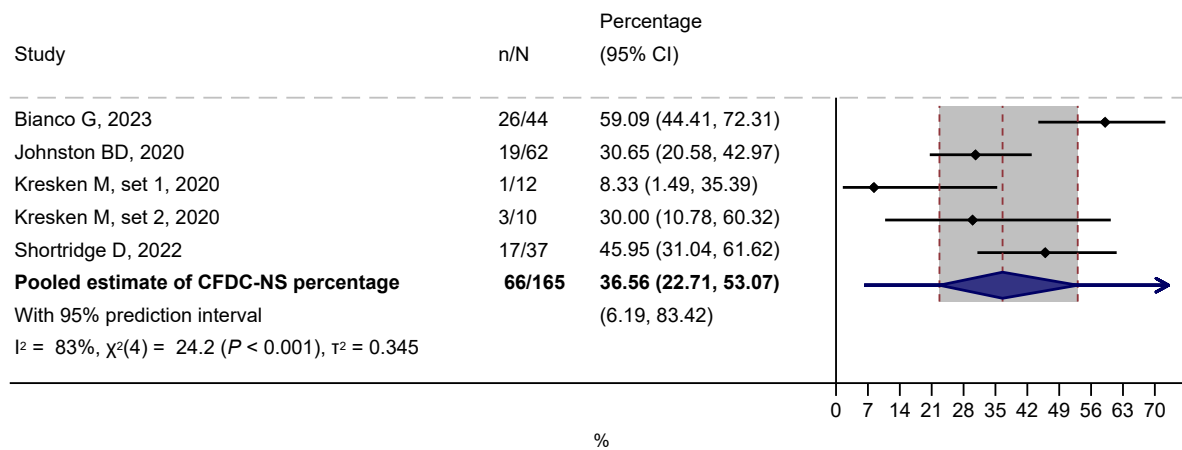
Note. n is the number of NDM-producing Enterobacterales isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to EUCAST breakpoints. N is the overall number of NDM-producing Enterobacterales clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

8.2.9 Enterobacterales, CZA-resistant; CLSI-FDA



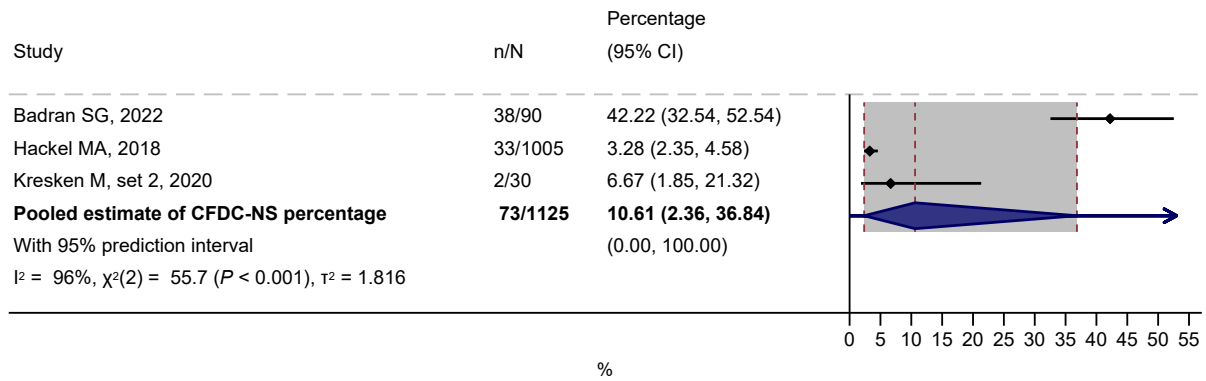
Note. n is the number of CZA-resistant Enterobacterales isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to CLSI-FDA breakpoints. N is the overall number of CZA-resistant Enterobacterales clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

8.2.10 Enterobacterales, CZA-resistant; EUCAST



Note. n is the number of CZA-resistant Enterobacterales isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to EUCAST breakpoints. N is the overall number of CZA-resistant Enterobacterales clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

8.2.11 Enterobacterales, CTA-resistant; CLSI-FDA



Note. n is the number of CTA-resistant Enterobacterales isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to CLSI-FDA breakpoints. N is the overall number of CTA-resistant Enterobacterales clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

9 Meta-analysis of cefiderocol non-susceptibility in different Enterobacterales species

Klebsiella spp.	Breakpoints	S	n/N	CFDC-NS %	Lower CL, %	Upper CL, %	I², %	τ²	Lower PL, %	Upper PL, %
Any phenotype	CLSI-FDA	20	47/6121	0.1	0.0	0.9	66	10.769	0.0	64.0
	EUCAST	13	286/6600	2.7	1.0	7.0	96	2.731	0.1	55.5
CR	CLSI-FDA	24	131/3320	1.8	0.7	4.3	86	3.843	0.0	54.0
	EUCAST	20	379/2114	10.6	5.2	20.3	96	2.524	0.4	78.7
MBL-producing	CLSI-FDA	11	34/269	4.1	1.1	14.4	85	2.878	0.1	72.9
	EUCAST	11	54/272	8.9	2.6	26.4	92	3.273	0.1	88.4
E. coli										
Any phenotype	CLSI-FDA	16	32/6658	0.3	0.1	1.2	56	6.897	0.0	50.1
	EUCAST	13	79/7498	1.0	0.3	3.6	85	5.584	0.0	69.0
CR	CLSI-FDA	15	107/763	4.3	1.3	12.8	90	2.930	0.1	69.2
	EUCAST	15	147/793	10.8	4.8	22.9	91	1.863	0.5	73.1
MBL-producing	CLSI-FDA	9	62/233	14.0	3.4	42.8	96	4.185	0.1	96.6
	EUCAST	9	96/231	36.3	15.3	64.3	96	2.588	1.0	97.0
Enterobacter spp.										
Any phenotype	CLSI-FDA	14	16/2620	0.3	0.1	1.7	21	5.712	0.0	45.2
	EUCAST	9	66/1644	3.0	0.6	12.9	86	3.802	0.0	81.9
CR	CLSI-FDA	15	44/626	6.5	3.2	12.8	70	0.940	0.7	39.8
	EUCAST	11	51/233	22.6	15.6	31.6	66	0.173	9.0	46.2
MBL-producing	CLSI-FDA	7	22/152	15.7	3.9	45.9	85	3.027	0.1	96.1
	EUCAST	6	28/108	30.6	16.6	49.4	78	0.310	6.1	74.9
Proteus spp.										
Any phenotype	CLSI-FDA	3	2/66	3.0	0.8	11.3	0	0.000	0.1	40.7
	EUCAST	4	6/664	2.1	0.2	16.1	0	4.234	0.0	97.4
CR	CLSI-FDA	3	1/25	4.0	0.6	23.5	0	0.000	0.0	100.0
	EUCAST	2	0/17	0.0	.	.	0	0.542	.	.

Serratia spp.	Breakpoints	S	n/N	CFDC-NS %	Lower CL, %	Upper CL, %	I², %	τ²	Lower PL, %	Upper PL, %
Any phenotype	CLSI-FDA	10	10/2009	0.4	0.1	1.6	0	2.701	0.0	19.4
	EUCAST	7	10/1851	0.5	0.3	1.0	15	0.000	0.2	1.2
CR	CLSI-FDA	1	5/5
	EUCAST	3	3/16	18.8	6.2	44.8	15	0.000	1.4	78.4
Citrobacter spp.										
Any phenotype	CLSI-FDA	9	5/1160	0.4	0.2	1.0	0	0.000	0.1	1.2
	EUCAST	4	11/899	1.9	0.5	6.6	0	0.441	0.0	52.0
Morganella spp.										
Any phenotype	CLSI-FDA	3	0/24	0.0	.	.	0	0.542	.	.
	EUCAST	4	0/302	0.0	.	.	0	1.000	.	.

S is the number of independent datasets in the analysis (a single study may have contributed more than one sets of data). **n/N** is the ratio of the cumulative number of *Klebsiella* spp. isolates that were non-susceptible to Cefiderocol (**CFDC-NS**) over the total number of isolates, according to the respective definition of breakpoints and resistance phenotype. **CFDC-NS**, cefiderocol non-susceptible; **CL**, 95% confidence limit; **PL**, 95% prediction limit; **CAR**, carbapenem; **MBL**, metallo-β-lactamase; **NDM**, New Delhi metallo-β-lactamase; **CZA**, ceftazidime/avibactam; **CTA**, ceftolozane/tazobactam

10 Meta-analysis of cefiderocol non-susceptibility in *P. aeruginosa*

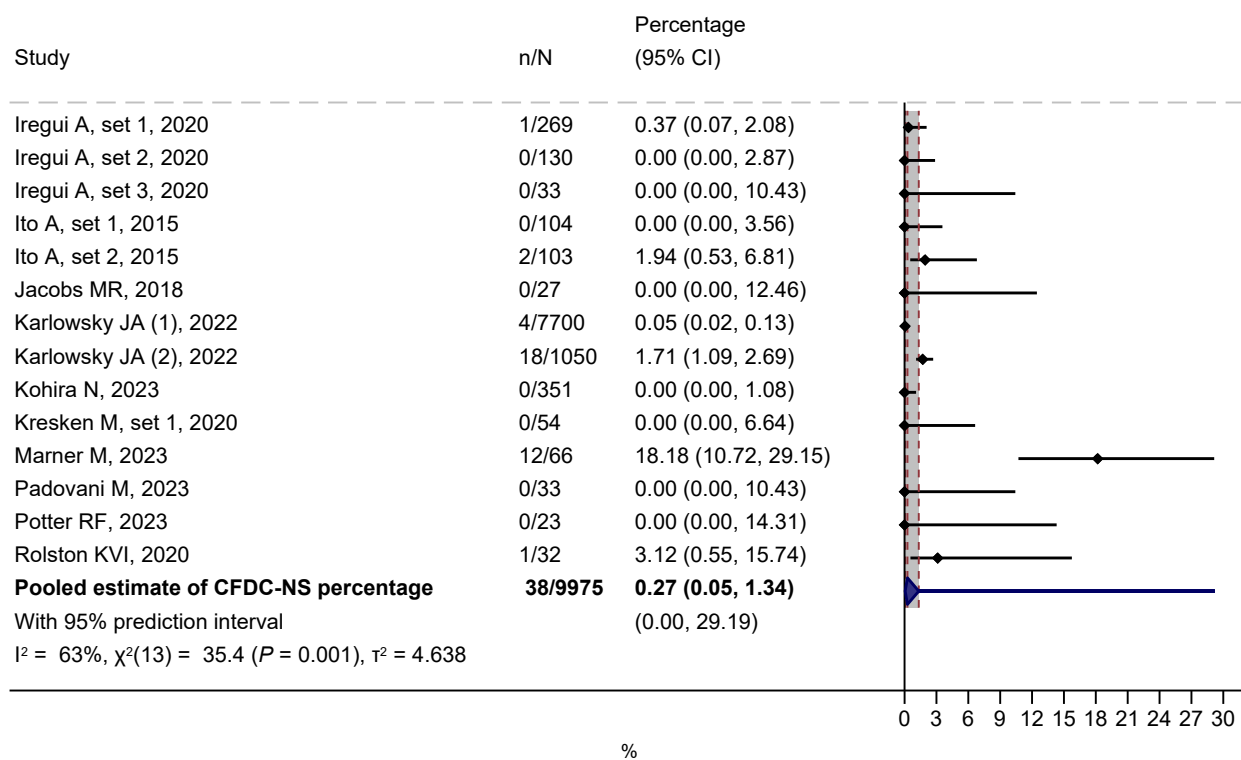
10.1 Summary table

<i>P. aeruginosa</i>	Breakpoints	S	n/N	CFDC-NS %	Lower CL, %	Upper CL, %	I ² , %	τ ²	Lower PL, %	Upper PL, %
Any phenotype	CLSI	14	38/9975	0.3	0.1	1.3	63	4.638	0.0	29.2
	EUCAST	15	174/11991	1.4	0.5	4.0	89	2.986	0.0	41.9
	FDA	11	487/11710	3.3	1.4	7.7	97	1.639	0.2	42.7
CR	CLSI	23	68/4389	0.8	0.3	2.2	64	3.361	0.0	30.4
	EUCAST	20	218/4041	3.5	1.6	7.8	91	2.849	0.1	58.8
	FDA	16	500/3653	14.6	7.5	26.3	97	1.954	0.8	79.2
MBL-producing	CLSI	13	22/562	1.6	0.3	7.8	53	5.045	0.0	74.9
	EUCAST	12	32/527	1.8	0.3	10.4	74	8.010	0.0	92.8
	FDA	9	72/381	23.3	10.4	44.1	92	1.854	1.1	89.5
NDM-producing	CLSI	6	8/41	19.5	10.1	34.4	2	0.000	8.1	40.0
	EUCAST	7	14/51	22.9	8.1	49.7	67	1.339	1.2	88.0
	FDA	6	25/41	58.7	20.4	88.7	90	3.413	0.7	99.6
CZA-resistant	CLSI	7	22/1163	1.7	0.5	5.1	73	1.682	0.0	39.9
	EUCAST	5	54/519	6.8	3.1	14.6	87	0.505	0.5	50.8
	FDA	5	122/519	19.5	11.9	30.4	90	0.315	3.1	64.8
CTA-resistant	CLSI	8	20/1038	2.2	0.8	5.6	59	1.322	0.1	32.3
	EUCAST	6	41/376	8.3	4.1	16.0	75	0.432	1.1	42.7
	FDA	6	81/376	15.1	7.4	28.2	90	0.678	1.4	69.4

S is the number of independent datasets in the analysis (a single study may have contributed more than one sets of data). **n/N** is the ratio of the cumulative number of *Klebsiella* spp. isolates that were non-susceptible to Cefiderocol (**CFDC-NS**) over the total number of isolates, according to the respective definition of breakpoints and resistance phenotype. **CFDC-NS**, cefiderocol non-susceptible; **CL**, 95% confidence limit; **PL**, 95% prediction limit; **CAR**, carbapenem; **MBL**, metallo-β-lactamase; **NDM**, New Delhi metallo-β-lactamase; **CZA**, ceftazidime/avibactam; **CTA**, ceftolozane/tazobactam

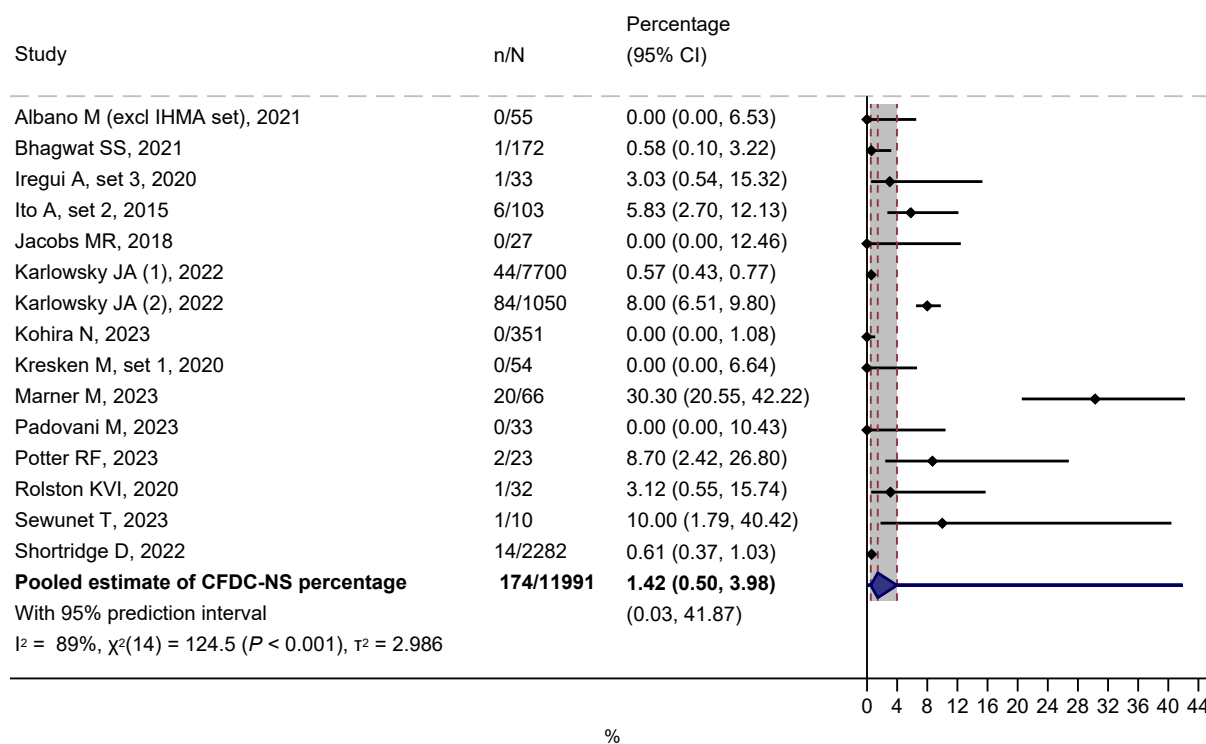
10.2 Forest plots

10.2.1 *P. aeruginosa*, any phenotype; CLSI



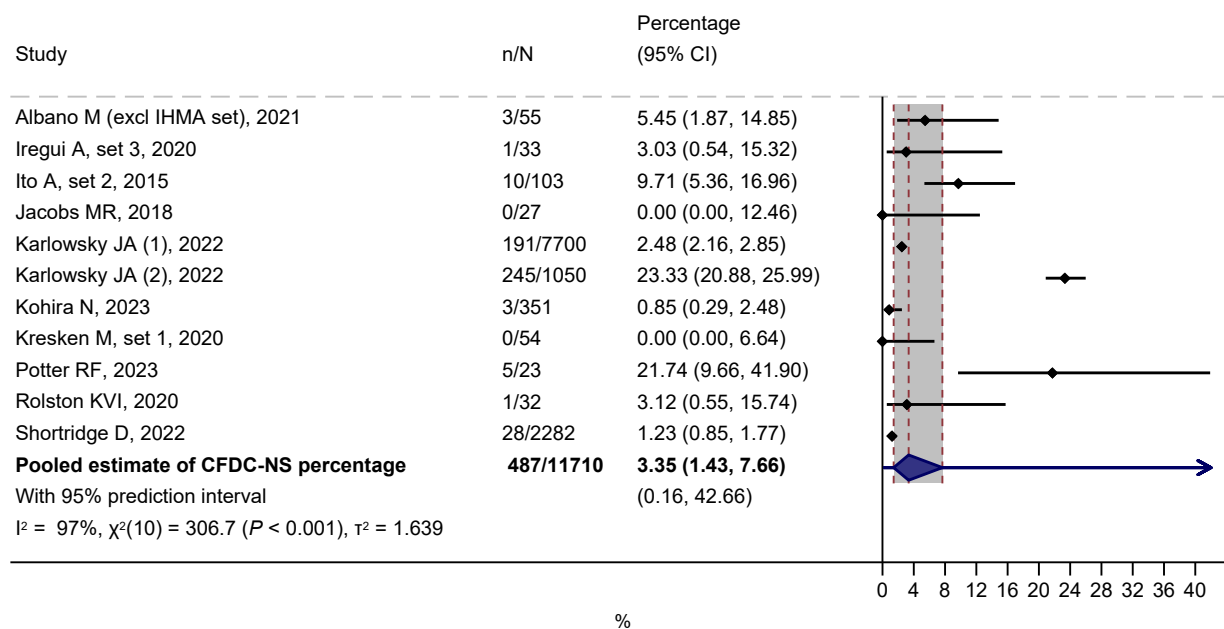
Note. n is the number of *P. aeruginosa* (any phenotype) isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to CLSI breakpoints. N is the overall number of *P. aeruginosa* (any phenotype) clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

10.2.2 *P. aeruginosa*, any phenotype; EUCAST



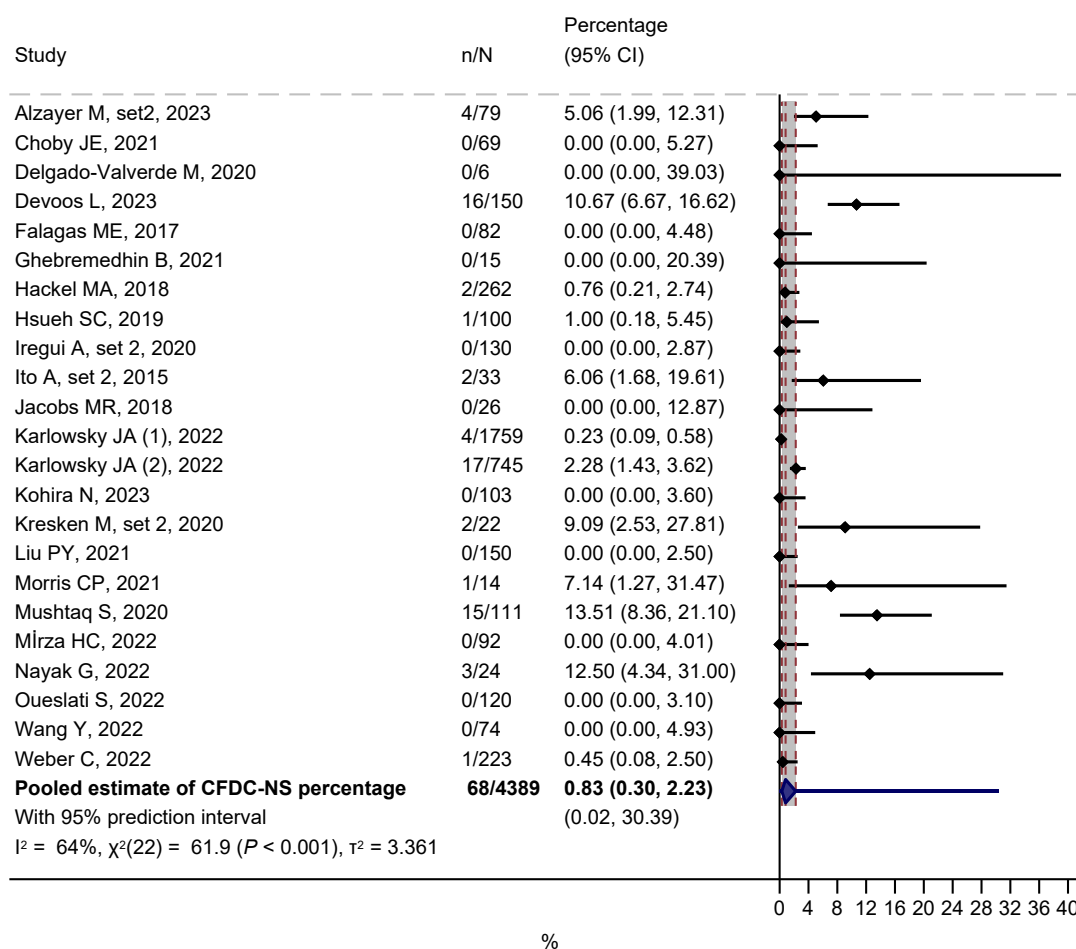
Note. n is the number of *P. aeruginosa* (any phenotype) isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to EUCAST breakpoints. N is the overall number of *P. aeruginosa* (any phenotype) clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

10.2.3 *P. aeruginosa*, any phenotype; FDA



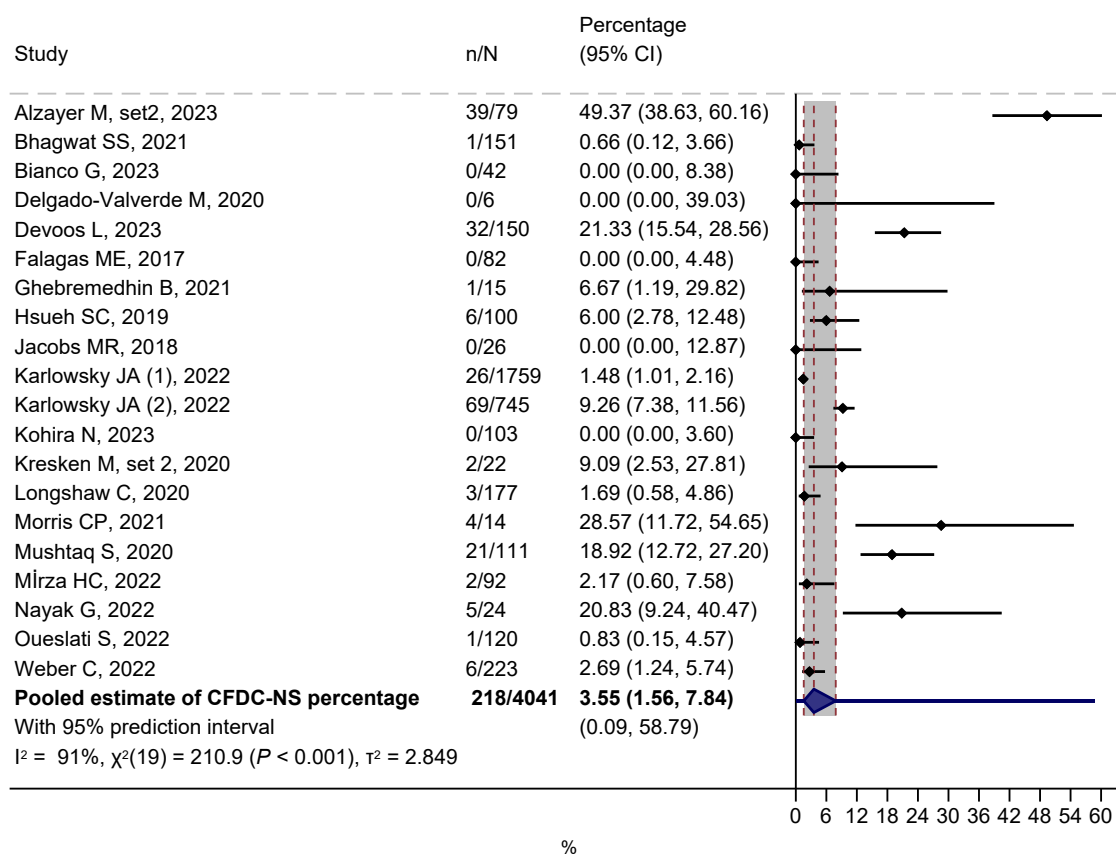
Note. n is the number of *P. aeruginosa* (any phenotype) isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to FDA breakpoints. N is the overall number of *P. aeruginosa* (any phenotype) clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

10.2.4 *P. aeruginosa*, carbapenem-resistant; CLSI



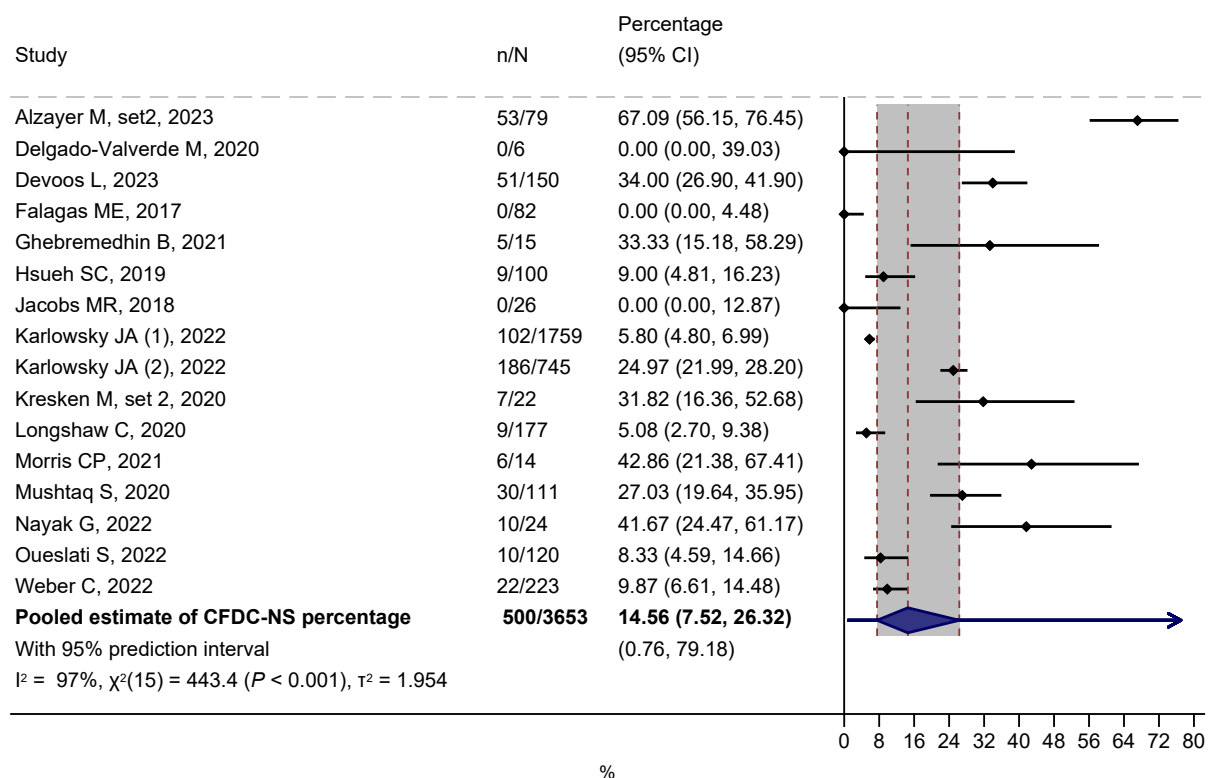
Note. n is the number of CR *P. aeruginosa* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to CLSI breakpoints. N is the overall number of CR *P. aeruginosa* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

10.2.5 *P. aeruginosa*, carbapenem-resistant; EUCAST



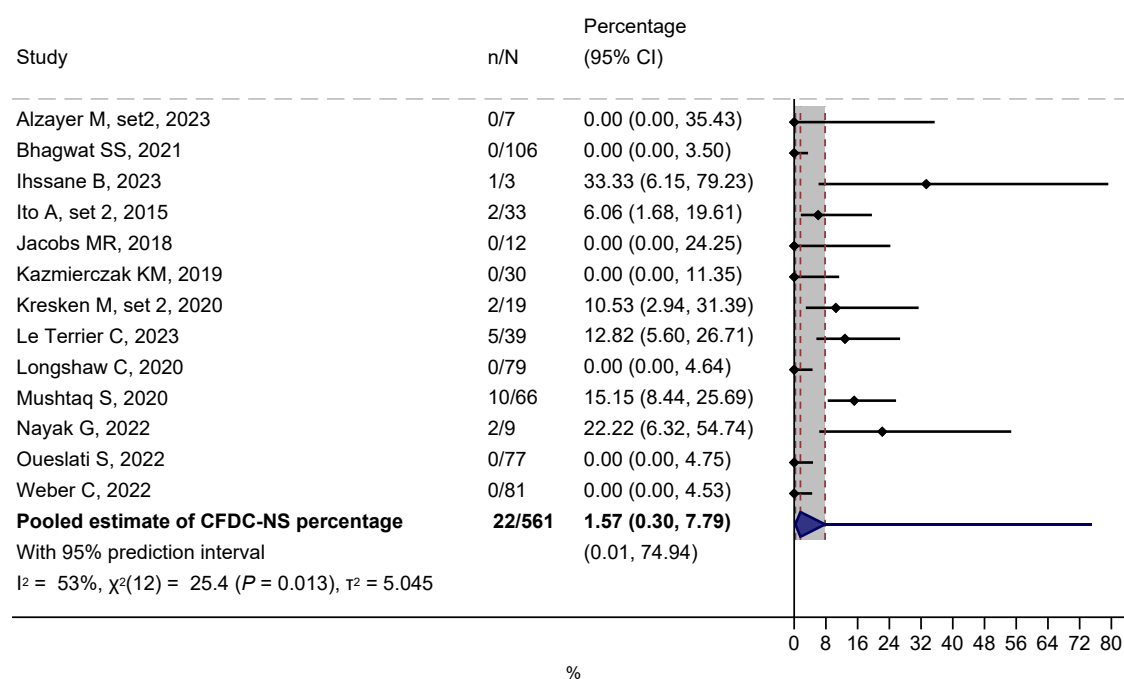
Note. n is the number of CR *P. aeruginosa* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to EUCAST breakpoints. N is the overall number of CR *P. aeruginosa* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

10.2.6 *P. aeruginosa*, carbapenem-resistant; FDA



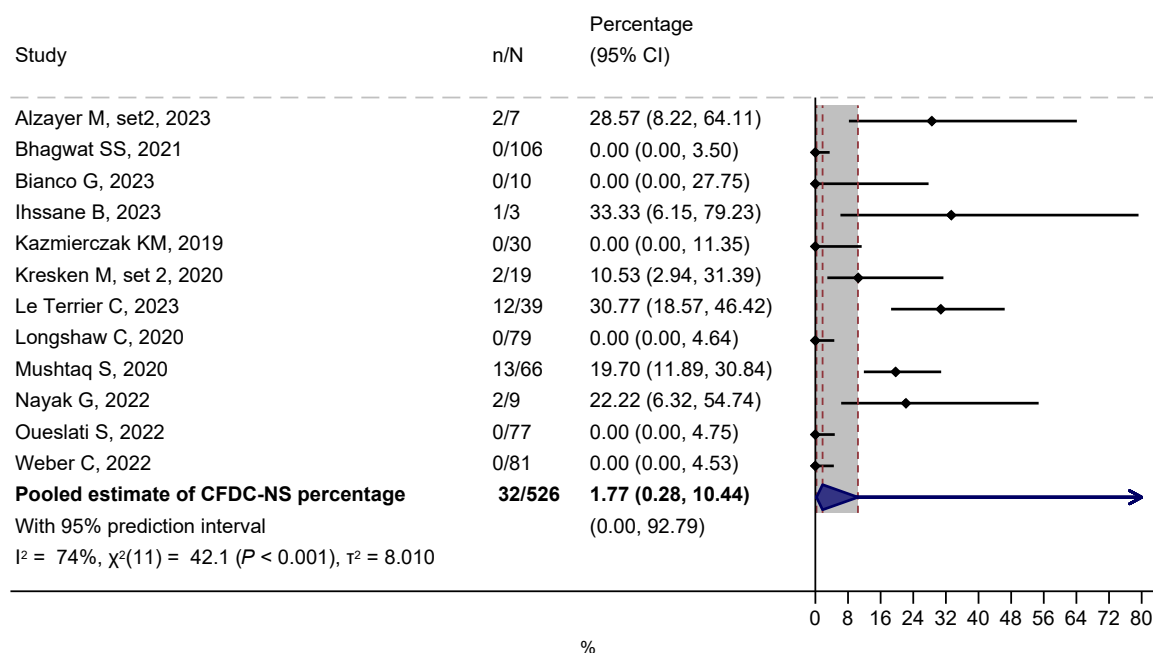
Note. n is the number of CR *P. aeruginosa* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to FDA breakpoints. N is the overall number of CR *P. aeruginosa* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

10.2.7 *P. aeruginosa*, MBL-producing; CLSI



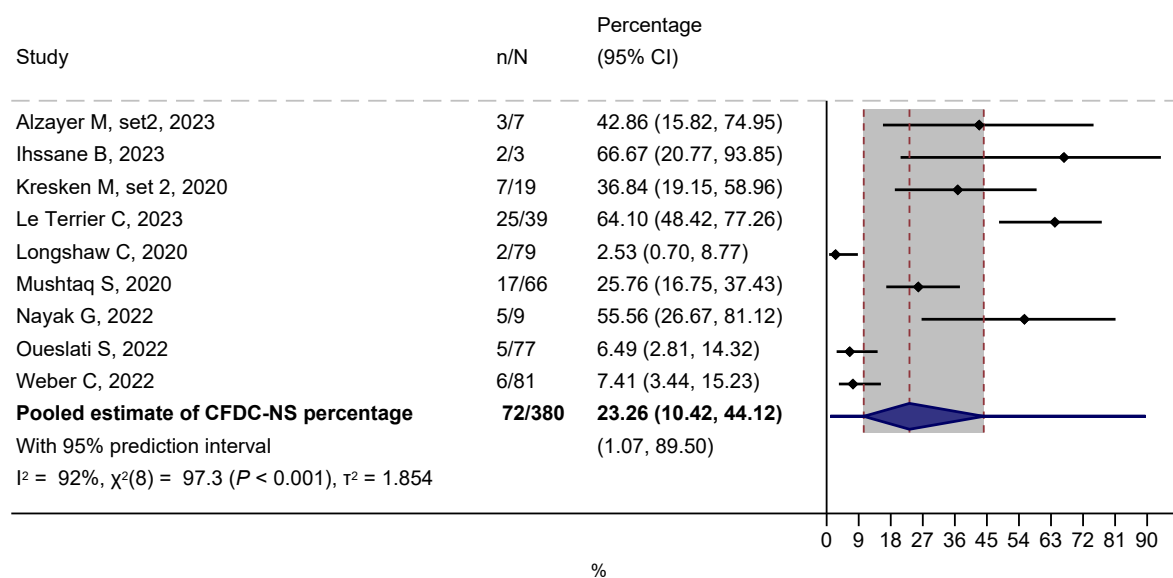
Note. n is the number of MBL-producing *P. aeruginosa* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to CLSI breakpoints. N is the overall number of MBL-producing *P. aeruginosa* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

10.2.8 *P. aeruginosa*, MBL-producing; EUCAST



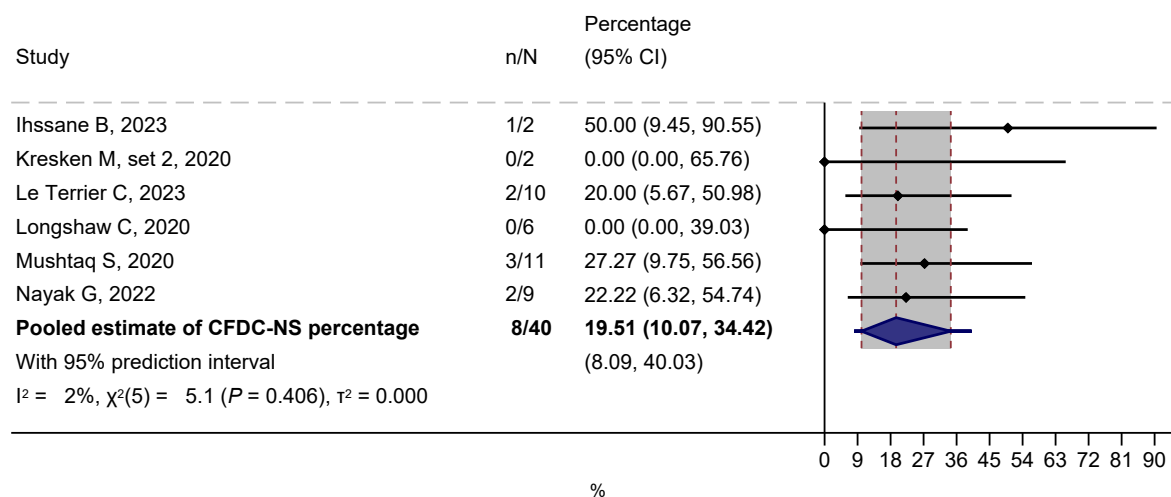
Note. n is the number of MBL-producing *P. aeruginosa* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to EUCAST breakpoints. N is the overall number of MBL-producing *P. aeruginosa* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

10.2.9 *P. aeruginosa*, MBL-producing; FDA



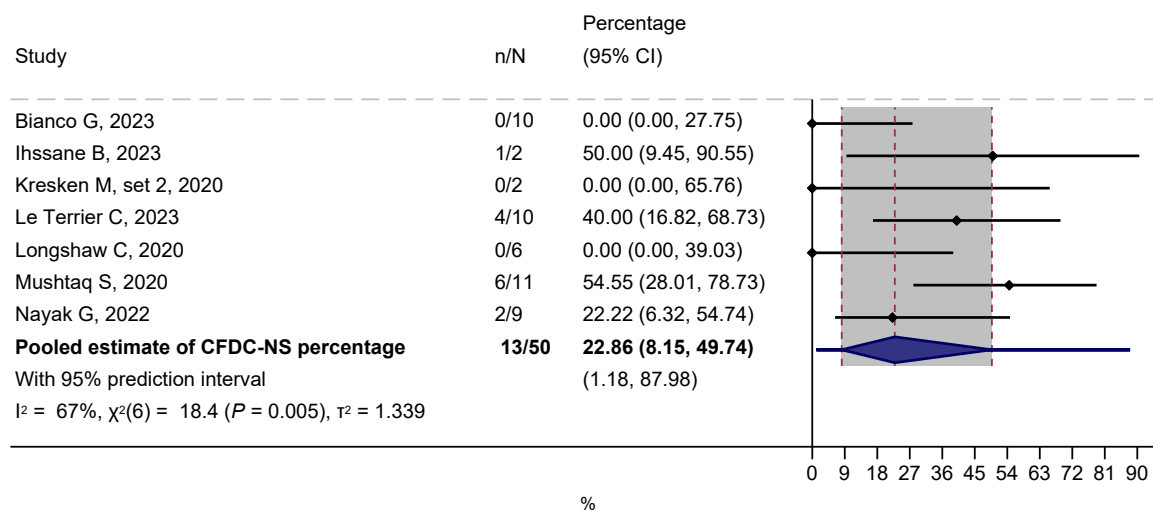
Note. n is the number of MBL-producing *P. aeruginosa* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to FDA breakpoints. N is the overall number of MBL-producing *P. aeruginosa* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

10.2.10 *P. aeruginosa*, NDM-producing; CLSI



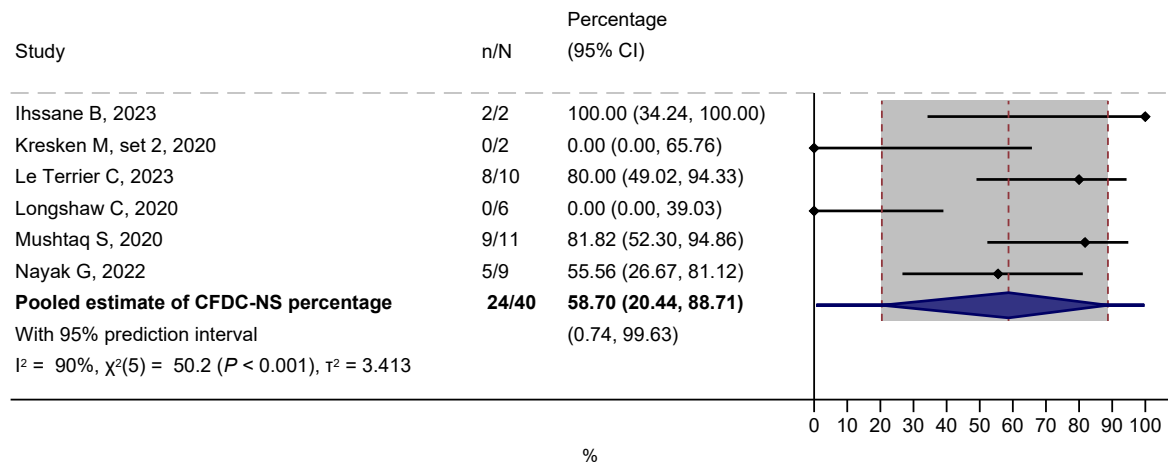
Note. n is the number of NDM-producing *P. aeruginosa* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to CLSI breakpoints. N is the overall number of NDM-producing *P. aeruginosa* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

10.2.11 *P. aeruginosa*, NDM-producing; EUCAST



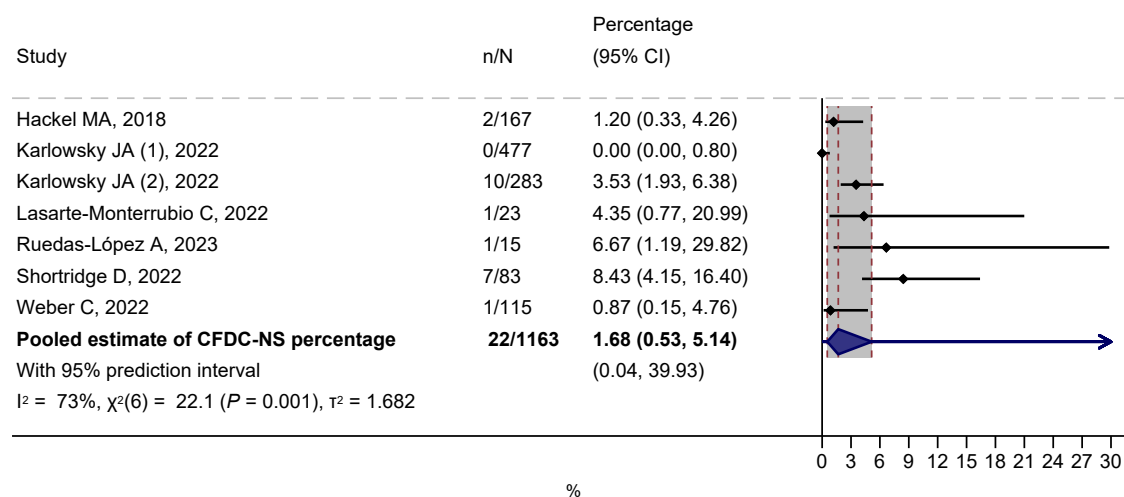
Note. n is the number of NDM-producing *P. aeruginosa* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to EUCAST breakpoints. N is the overall number of NDM-producing *P. aeruginosa* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

10.2.12 *P. aeruginosa*, NDM-producing; FDA



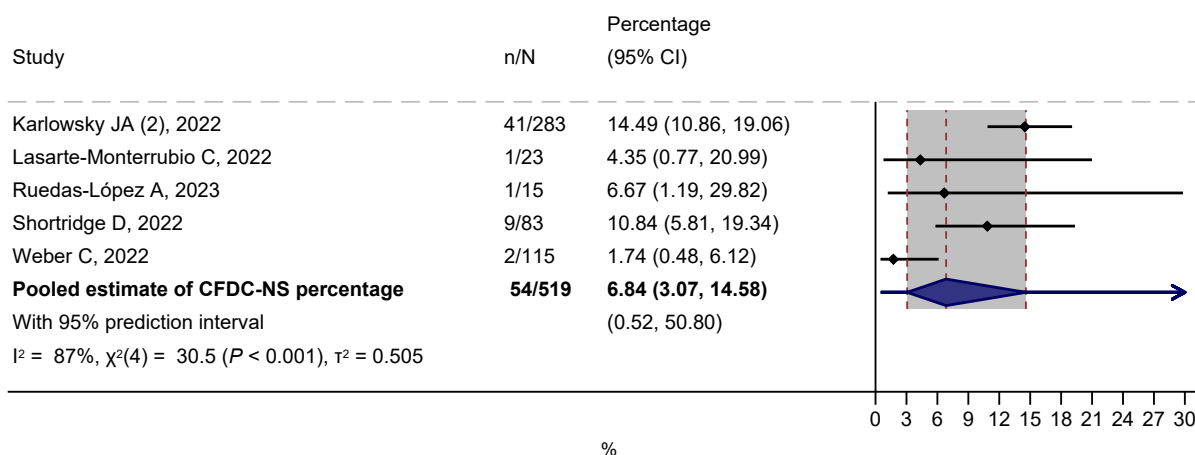
Note. n is the number of NDM-producing *P. aeruginosa* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to FDA breakpoints. N is the overall number of NDM-producing *P. aeruginosa* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

10.2.13 *P. aeruginosa*, CZA-resistant; CLSI



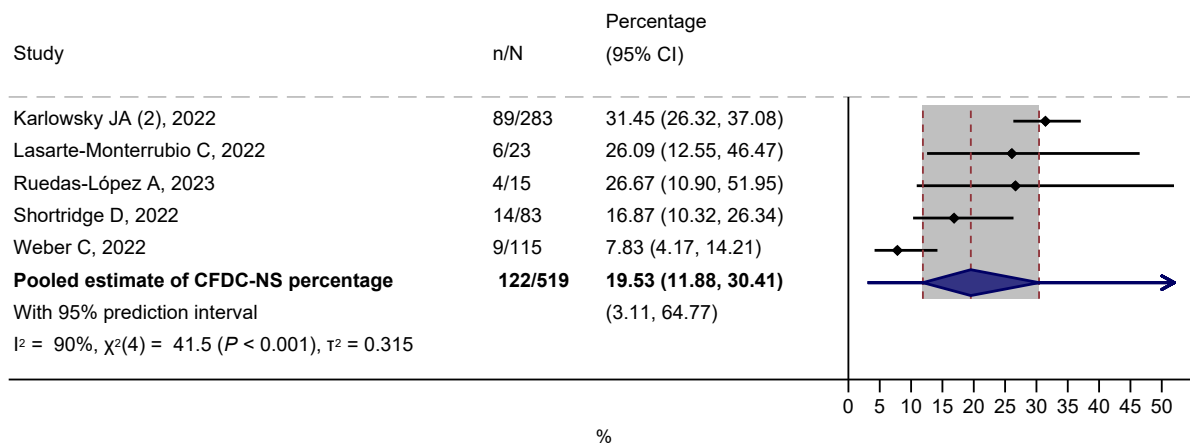
Note. n is the number of CZA-resistant *P. aeruginosa* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to CLSI breakpoints. N is the overall number of CZA-resistant *P. aeruginosa* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

10.2.14 *P. aeruginosa*, CZA-resistant; EUCAST

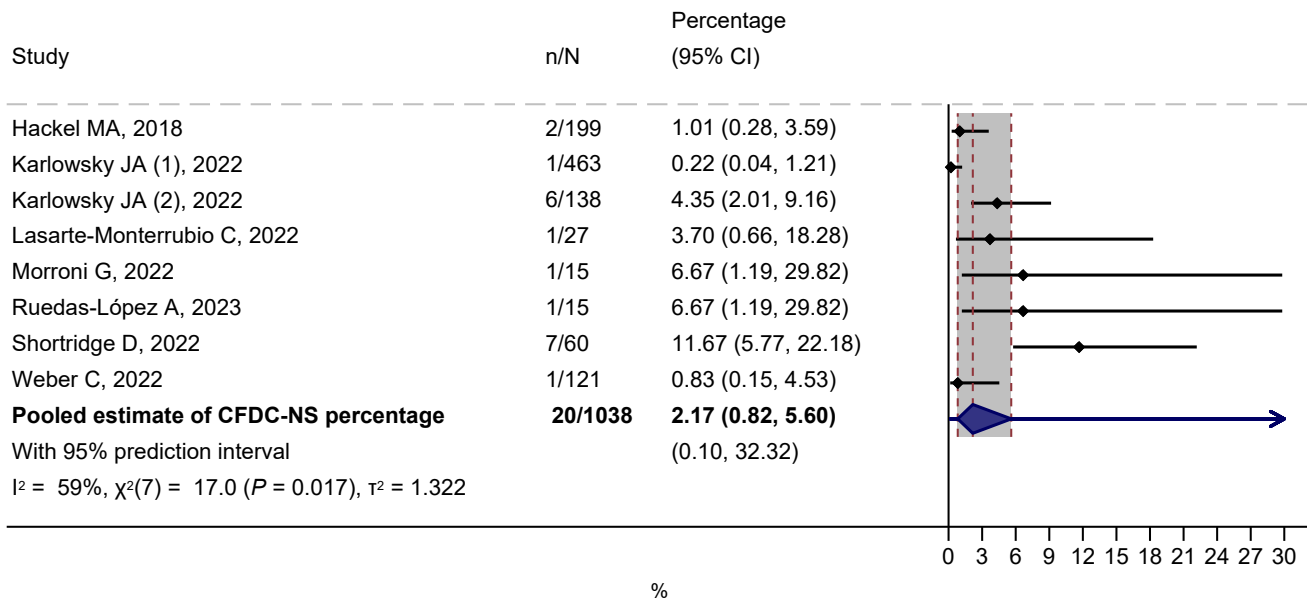


Note. n is the number of CZA-resistant *P. aeruginosa* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to EUCAST breakpoints. N is the overall number of CZA-resistant *P. aeruginosa* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

10.2.15 *P. aeruginosa*, CZA-resistant; FDA

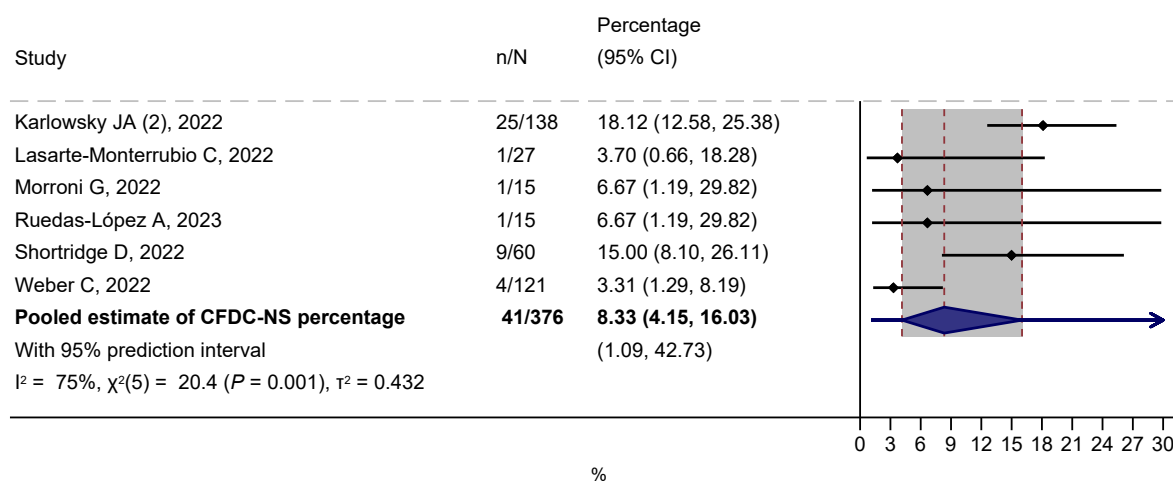


Note. n is the number of CZA-resistant *P. aeruginosa* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to FDA breakpoints. N is the overall number of CZA-resistant *P. aeruginosa* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

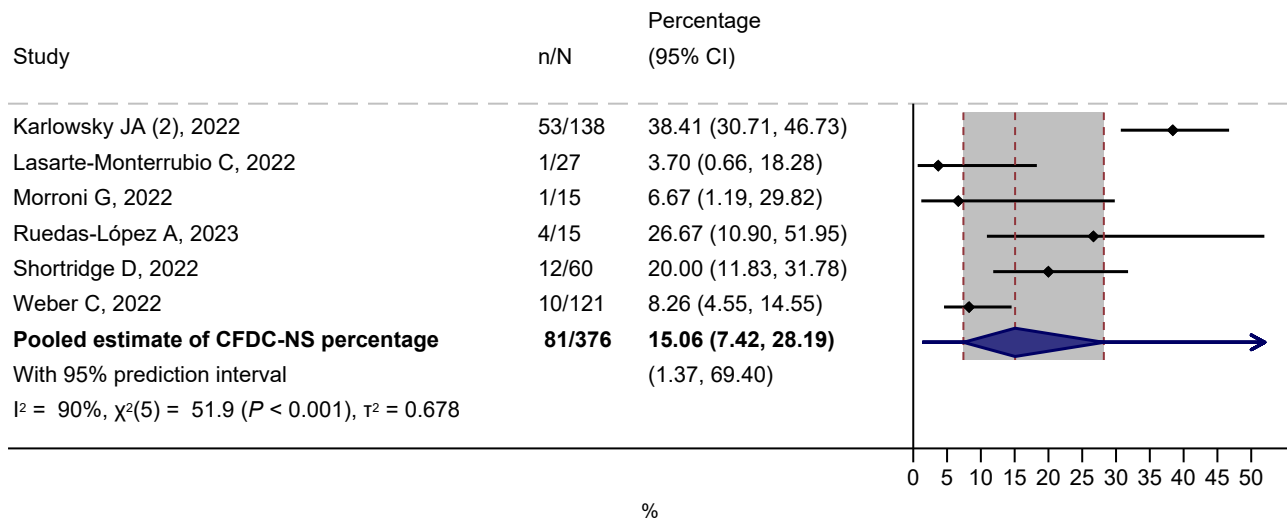


Note. n is the number of CTA-resistant *P. aeruginosa* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to CLSI breakpoints. N is the overall number of CTA-resistant *P. aeruginosa* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

10.2.17 *P. aeruginosa*, CTA-resistant; EUCAST



Note. n is the number of CTA-resistant *P. aeruginosa* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to EUCAST breakpoints. N is the overall number of CTA-resistant *P. aeruginosa* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.



Note. n is the number of CTA-resistant *P. aeruginosa* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to FDA breakpoints. N is the overall number of CTA-resistant *P. aeruginosa* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

11 Meta-analysis of cefiderocol non-susceptibility in *A. baumannii*

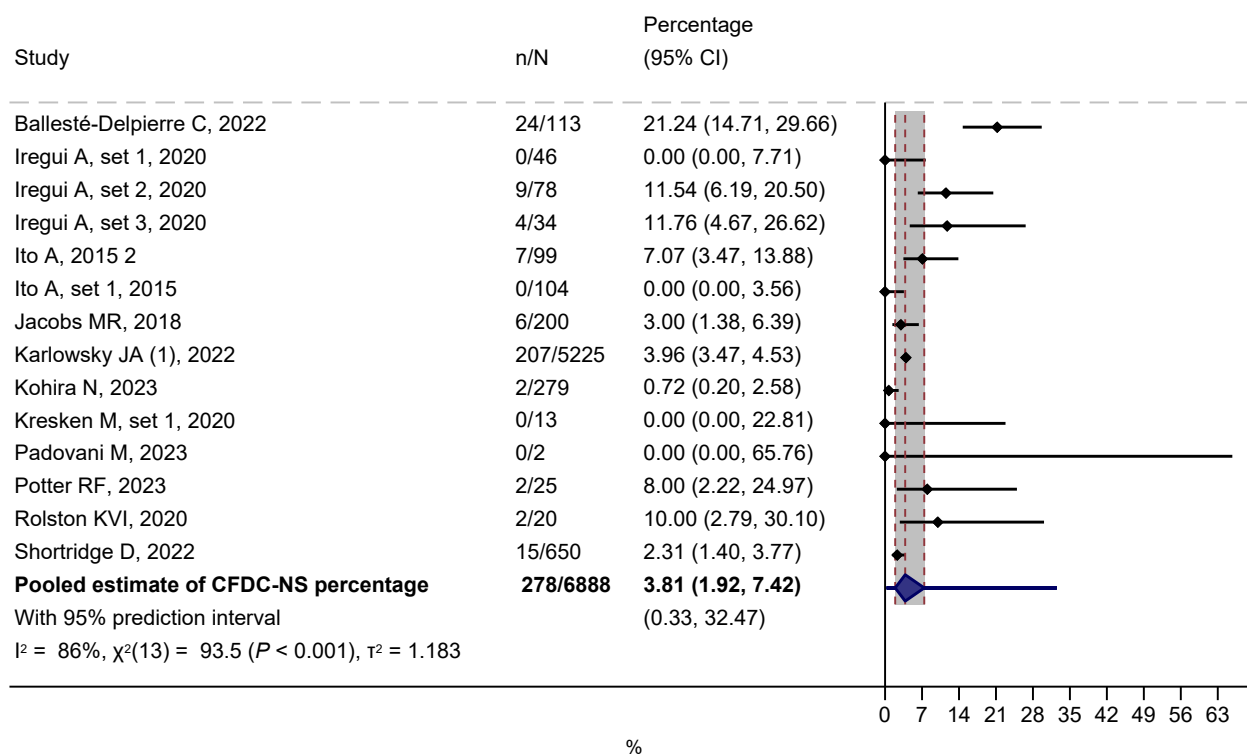
11.1 Summary table

<i>A. baumannii</i>	Breakpoints	S	n/N	CFDC-NS %	Lower CL, %	Upper CL, %	I ² , %	τ ²	Lower PL, %	Upper PL, %
Any phenotype	CLSI	14	278/6888	3.8	1.9	7.4	86	1.183	0.3	32.5
	EUCAST	13	422/6658	8.8	4.9	15.2	85	0.882	1.1	46.2
	FDA	12	725/6656	15.0	8.4	25.3	92	1.025	1.6	65.4
CR	CLSI	27	487/6047	8.5	5.7	12.5	91	1.027	1.1	44.1
	EUCAST	20	535/4831	13.2	7.8	21.5	95	1.524	1.0	68.7
	FDA	14	792/4171	26.6	18.3	36.9	95	0.698	5.1	70.7
MBL-producing	CLSI	9	19/93	20.4	13.4	29.8	58	0.000	12.3	32.0
	EUCAST	9	38/93	40.9	31.4	51.1	65	0.000	29.6	53.2
	FDA	9	61/93	53.1	21.5	82.4	86	2.953	1.4	98.9
NDM-producing	CLSI	8	19/85	23.0	13.6	36.3	67	0.146	8.0	50.7
	EUCAST	8	38/85	44.7	34.5	55.4	71	0.000	32.2	58.0
	FDA	8	60/85	71.3	21.7	95.7	90	8.076	0.1	100.0

S is the number of independent datasets in the analysis (a single study may have contributed more than one sets of data). **n/N** is the ratio of the cumulative number of *Klebsiella* spp. isolates that were non-susceptible to Cefiderocol (**CFDC-NS**) over the total number of isolates, according to the respective definition of breakpoints and resistance phenotype. **CFDC-NS**, cefiderocol non-susceptible; **CL**, 95% confidence limit; **PL**, 95% prediction limit; **CAR**, carbapenem; **MBL**, metallo-β-lactamase; **NDM**, New Delhi metallo-β-lactamase; **CZA**, ceftazidime/avibactam; **CTA**, ceftolozane/tazobactam

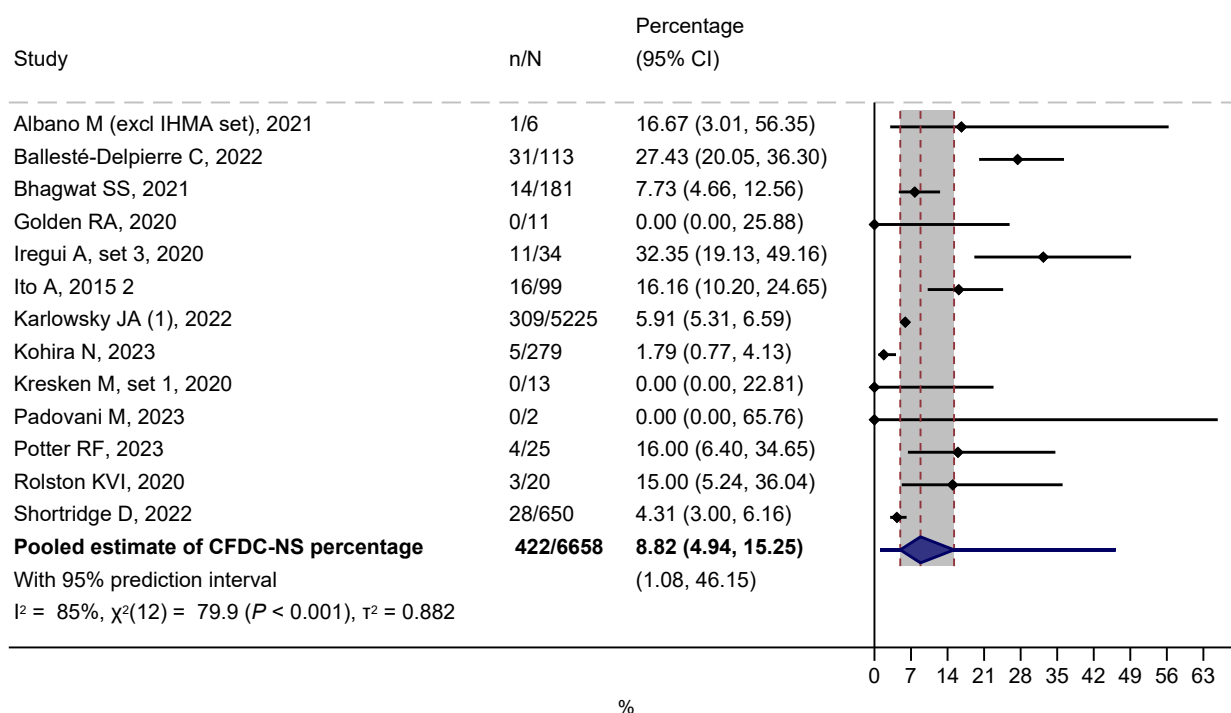
11.2 Forest plots

11.2.1 *A. baumannii*, any phenotype; CLSI



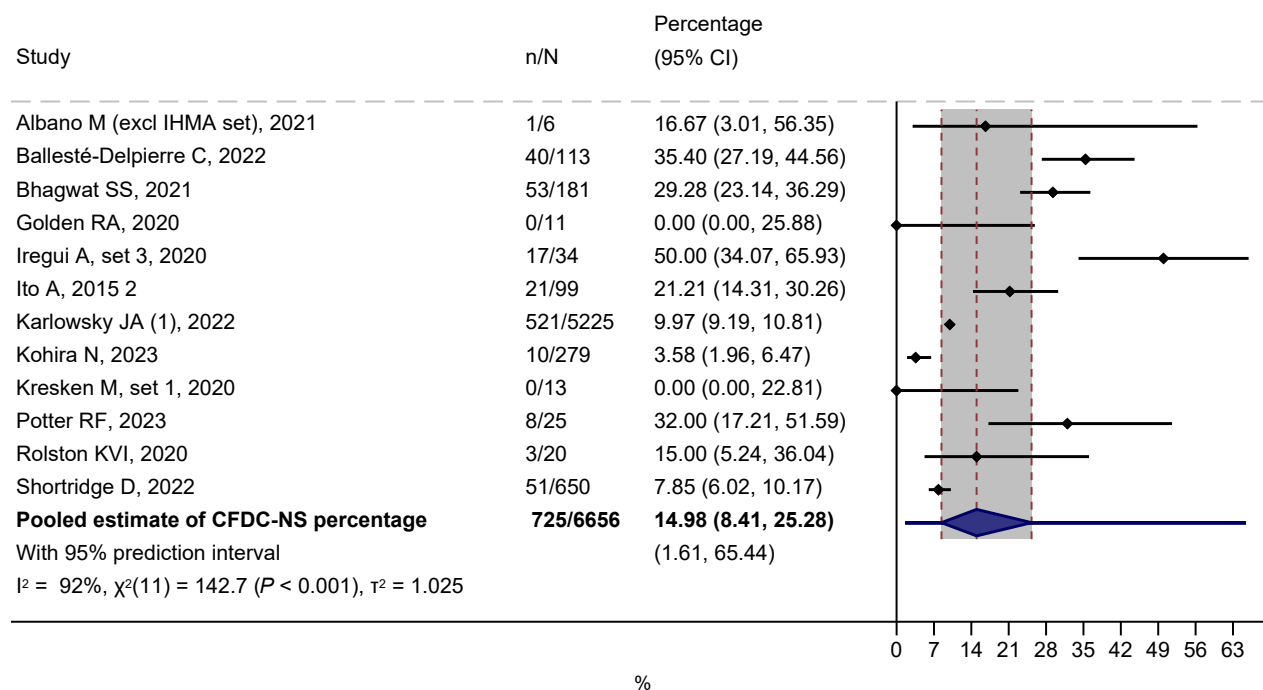
Note. n is the number of *A. baumannii* (any phenotype) isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to CLSI breakpoints. N is the overall number of *A. baumannii* (any phenotype) clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

11.2.2 *A. baumannii*, any phenotype; EUCAST



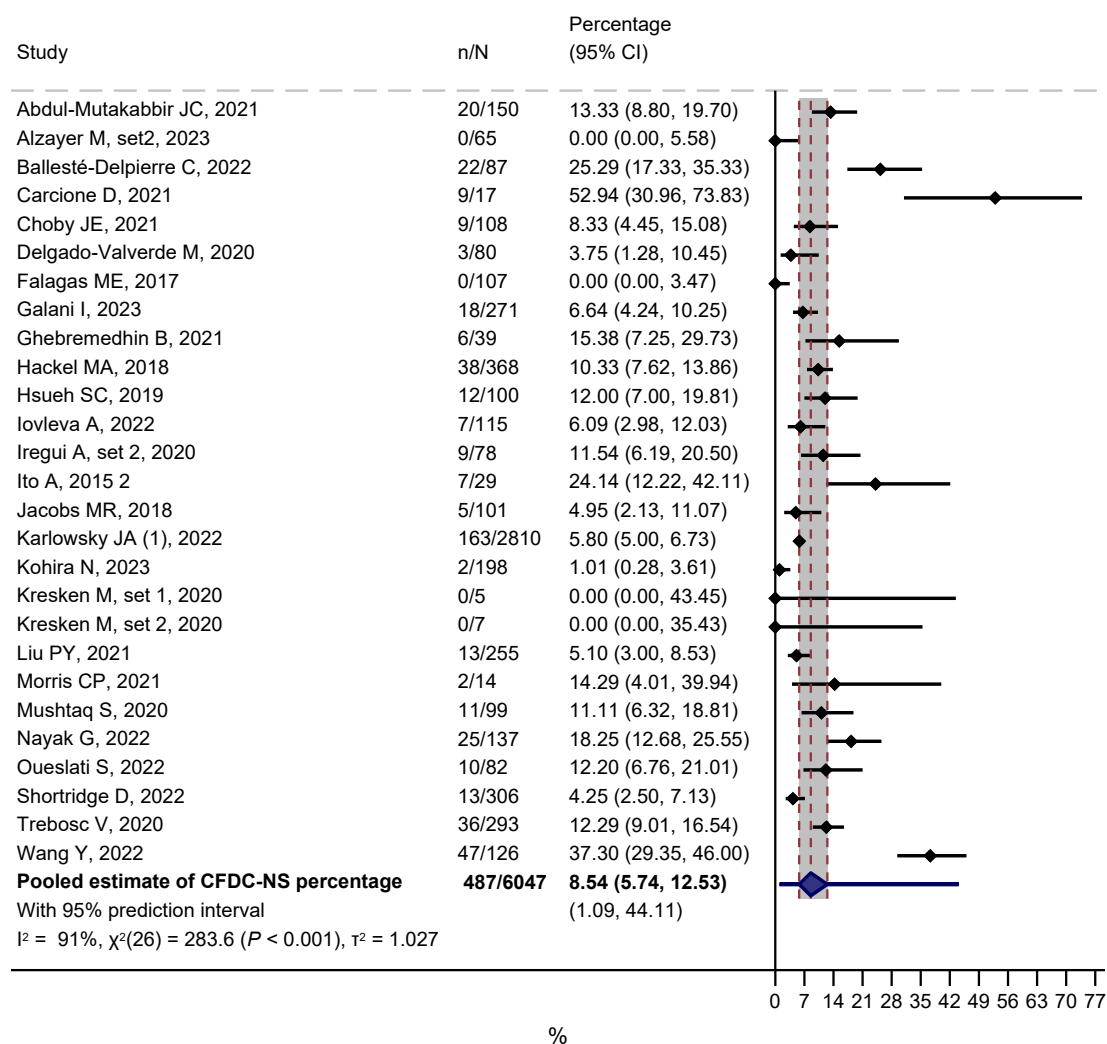
Note. n is the number of *A. baumannii* (any phenotype) isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to EUCAST breakpoints. N is the overall number of *A. baumannii* (any phenotype) clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

11.2.3 *A. baumannii*, any phenotype; FDA



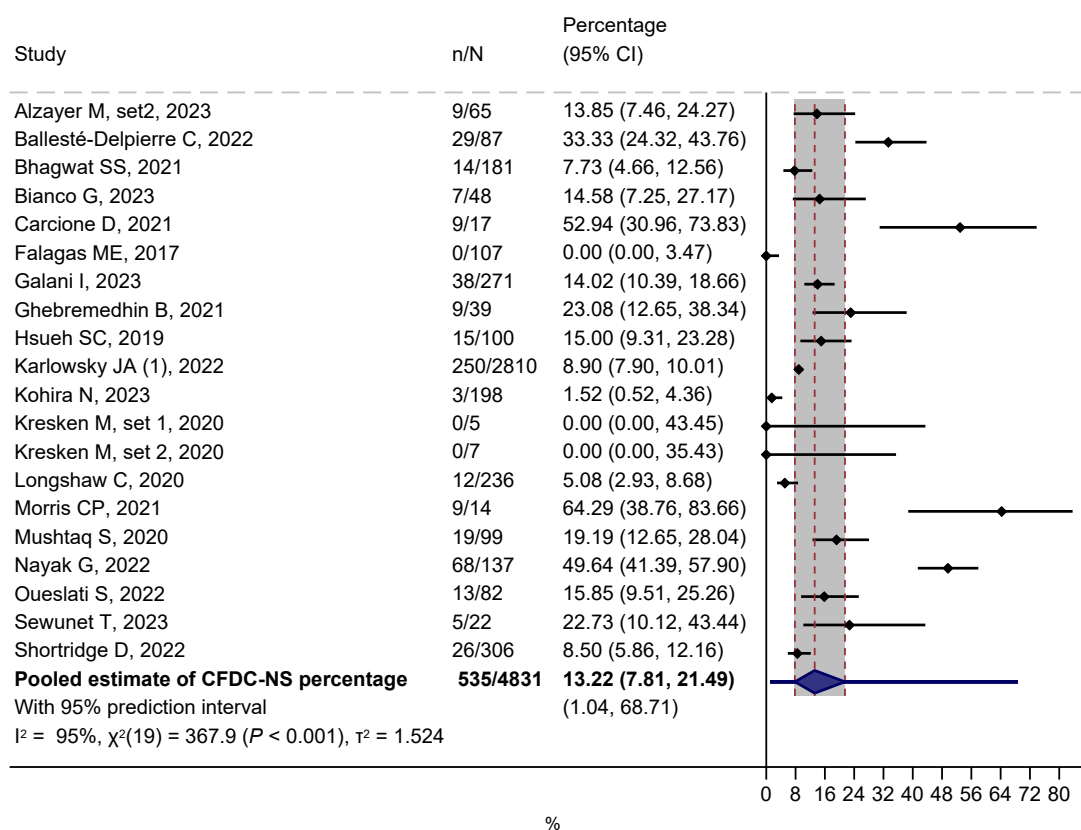
Note. n is the number of *A. baumannii* (any phenotype) isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to FDA breakpoints. N is the overall number of *A. baumannii* (any phenotype) clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

11.2.4 *A. baumannii*, carbapenem-resistant; CLSI



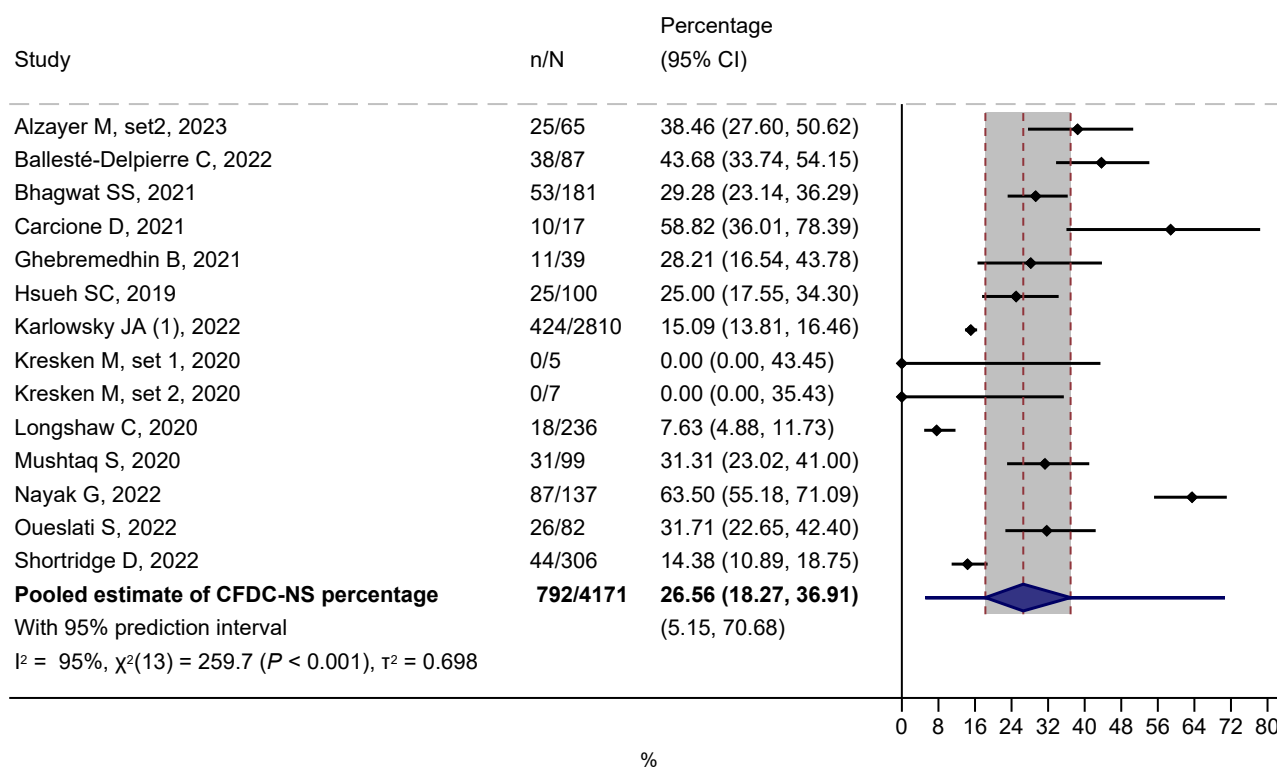
Note. n is the number of CR *A. baumannii* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to CLSI breakpoints. N is the overall number of CR *A. baumannii* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

11.2.5 *A. baumannii*, carbapenem-resistant; EUCAST



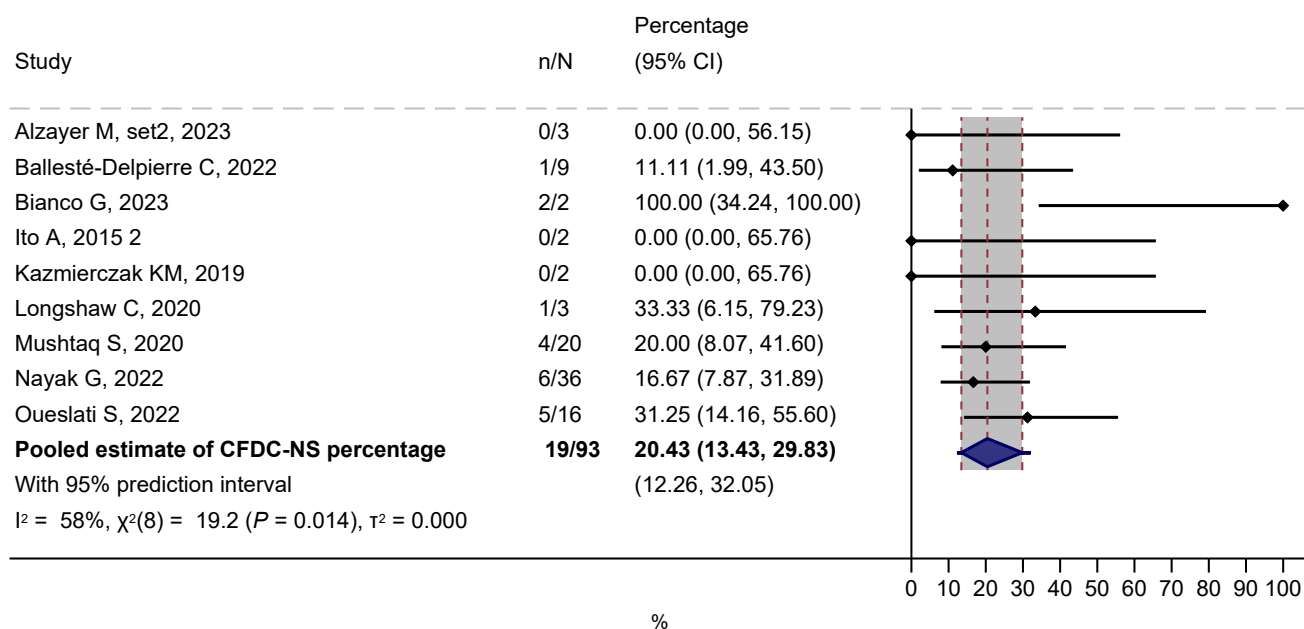
Note. n is the number of CR *A. baumannii* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to EUCAST breakpoints. N is the overall number of CR *A. baumannii* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

11.2.6 *A. baumannii*, carbapenem-resistant; FDA



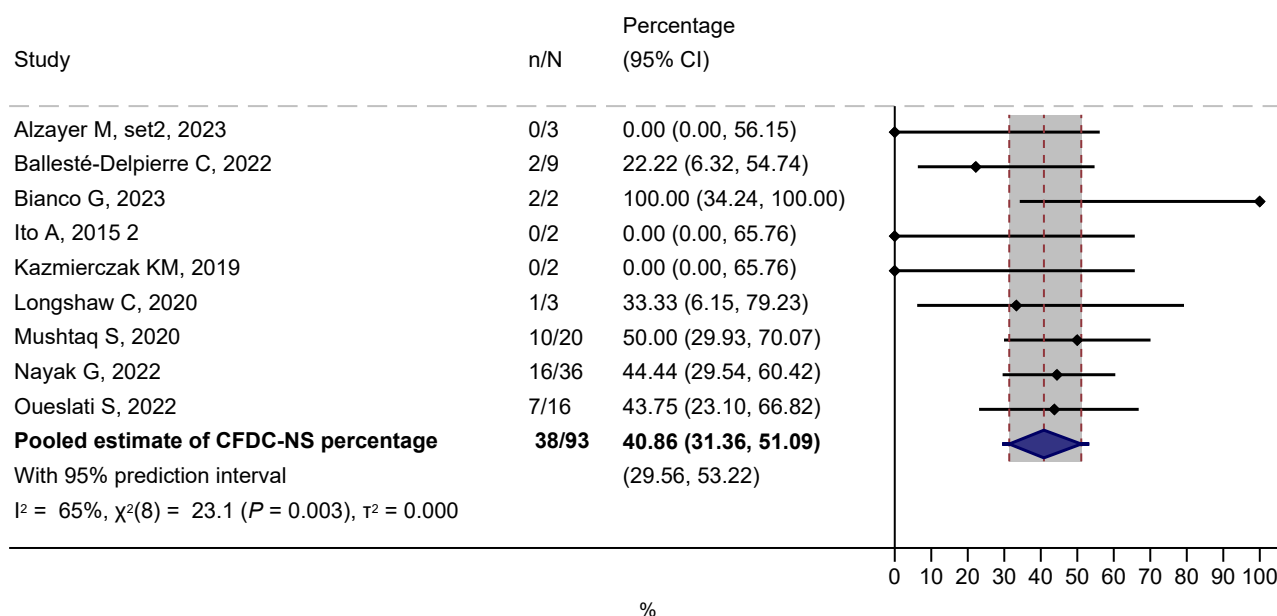
Note. n is the number of CR *A. baumannii* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to FDA breakpoints. N is the overall number of CR *A. baumannii* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

11.2.7 *A. baumannii*, MBL-producing; CLSI



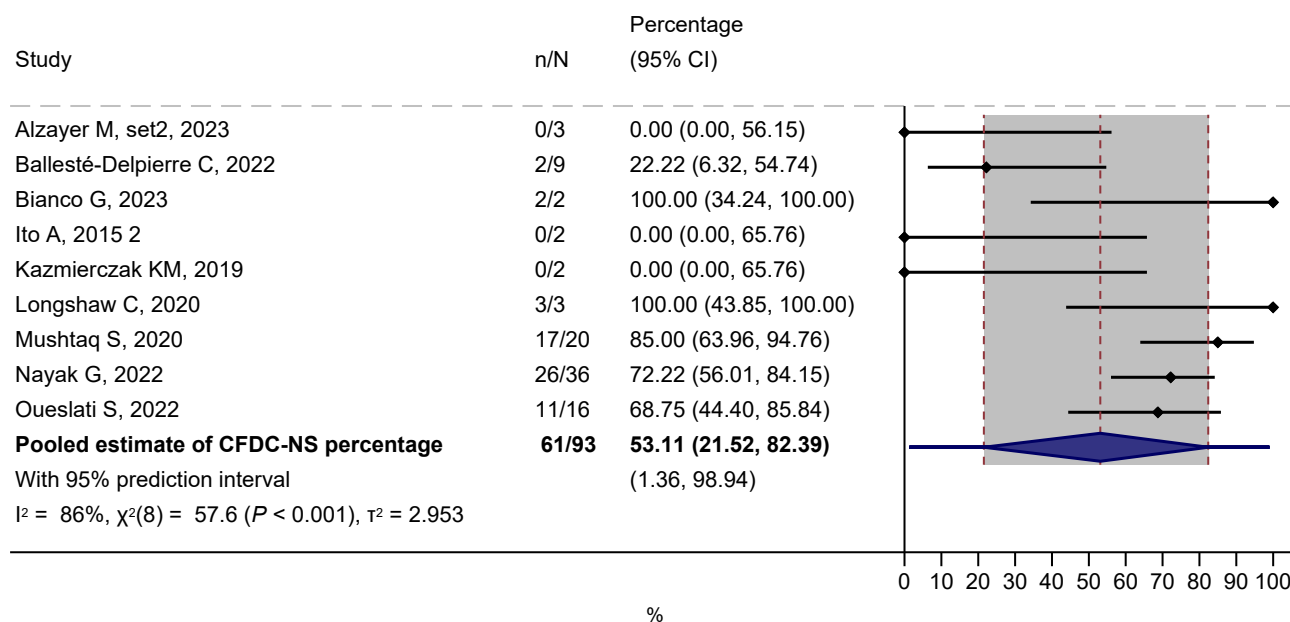
Note. n is the number of MBL-producing *A. baumannii* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to CLSI breakpoints. N is the overall number of MBL-producing *A. baumannii* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

11.2.8 *A. baumannii*, MBL-producing; EUCAST



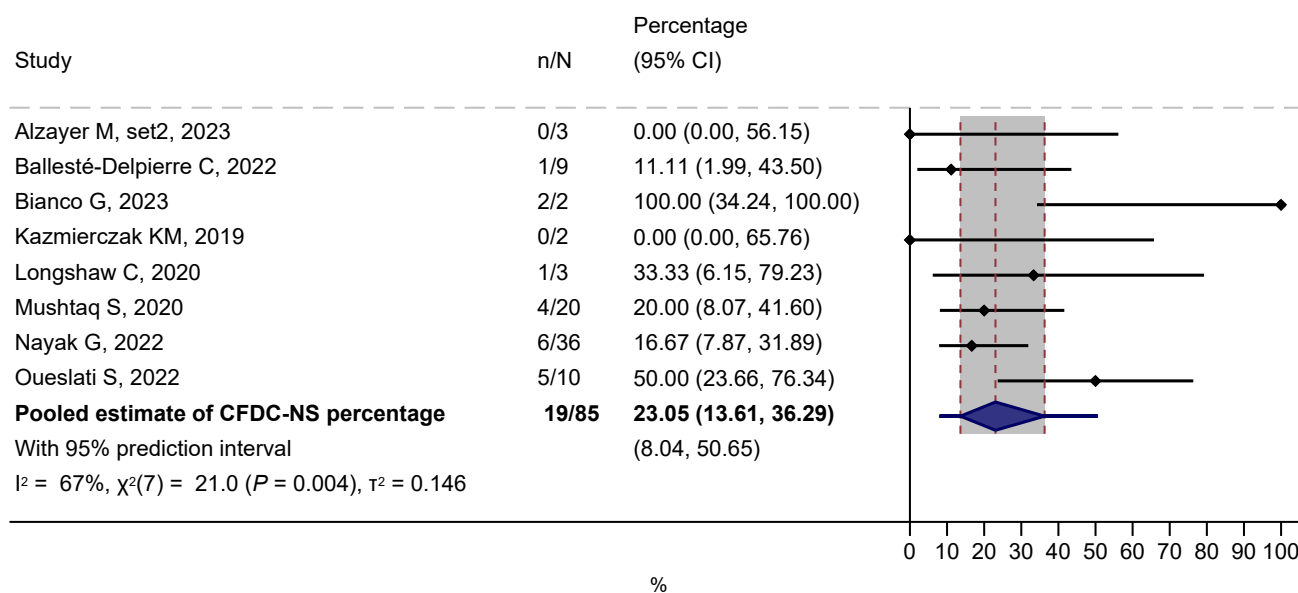
Note. n is the number of MBL-producing *A. baumannii* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to EUCAST breakpoints. N is the overall number of MBL-producing *A. baumannii* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

11.2.9 *A. baumannii*, MBL-producing; FDA



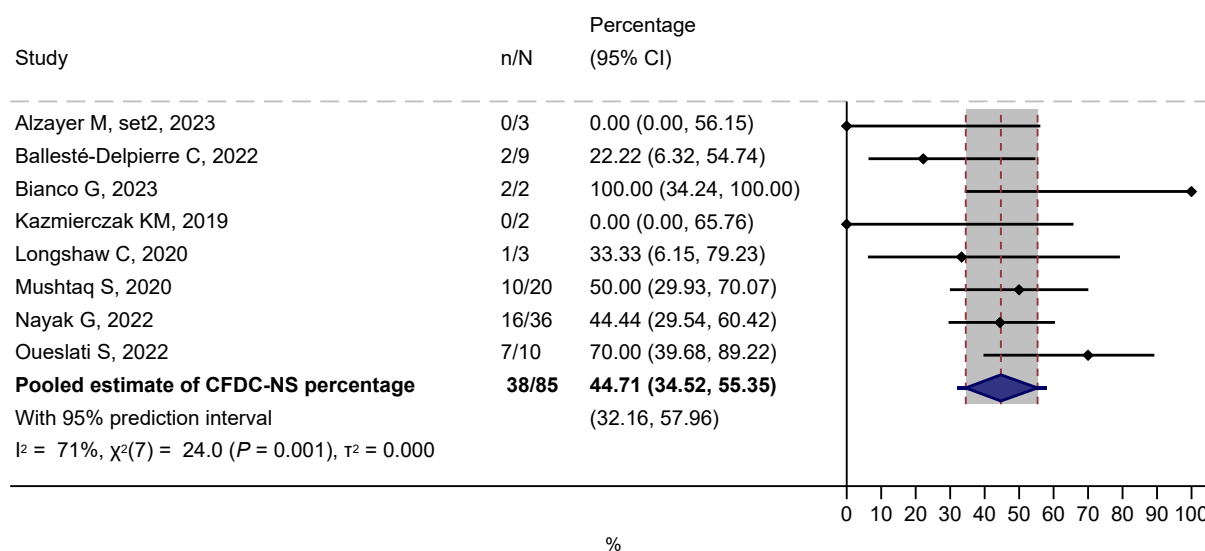
Note. n is the number of MBL-producing *A. baumannii* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to FDA breakpoints. N is the overall number of MBL-producing *A. baumannii* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

11.2.10 *A. baumannii*, NDM-producing; CLSI



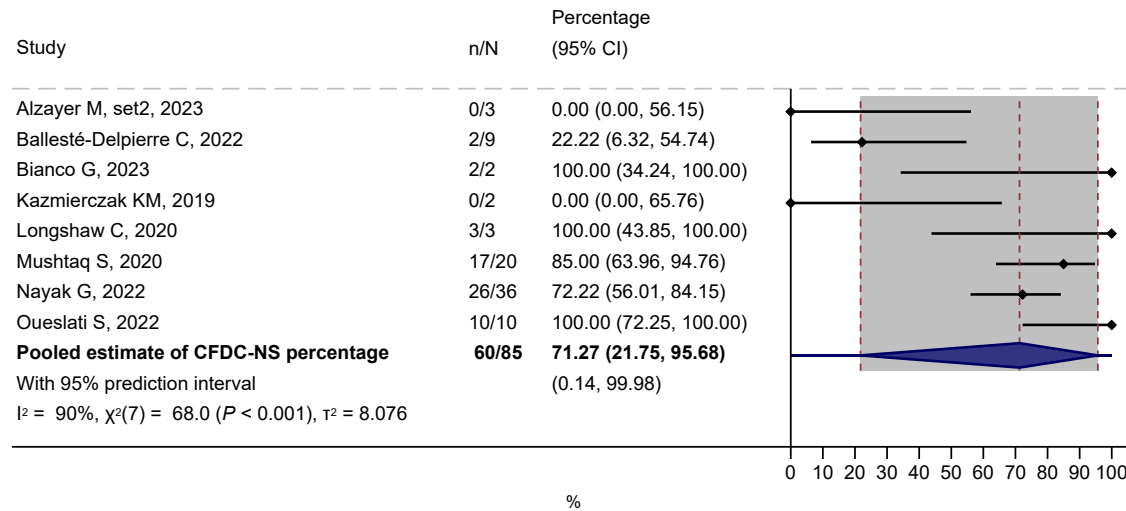
Note. n is the number of NDM-producing *A. baumannii* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to CLSI breakpoints. N is the overall number of NDM-producing *A. baumannii* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

11.2.11 *A. baumannii*, NDM-producing; EUCAST



Note. n is the number of NDM-producing *A. baumannii* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to EUCAST breakpoints. N is the overall number of NDM-producing *A. baumannii* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

11.2.12 *A. baumannii*, NDM-producing; FDA



Note. n is the number of NDM-producing *A. baumannii* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to FDA breakpoints. N is the overall number of NDM-producing *A. baumannii* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

12 Meta-analysis of cefiderocol non-susceptibility in *S. maltophilia*

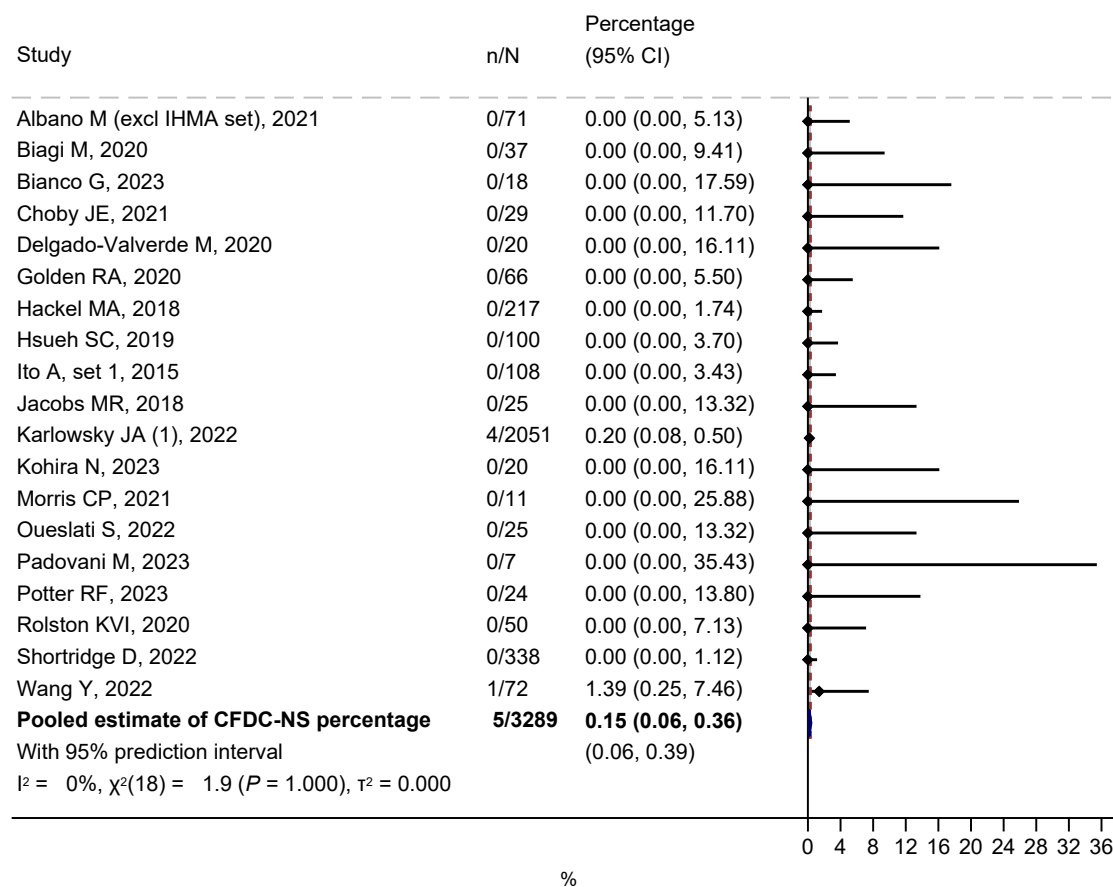
12.1 Summary table

<i>S. maltophilia</i>	Breakpoints	S	n/N	CFDC-NS %	Lower CL, %	Upper CL, %	I ² , %	τ ²	Lower PL, %	Upper PL, %
	CLSI old	19	5/3289	0.2	0.1	0.4	0	0.000	0.1	0.4
	CLSI new	13	81/3003	0.1	0.0	3.7	96	21.388	0.0	98.2
	EUCAST	15	11/3030	0.4	0.2	0.7	0	0.000	0.2	0.7

S is the number of independent datasets in the analysis (a single study may have contributed more than one sets of data). **n/N** is the ratio of the cumulative number of *Klebsiella* spp. isolates that were non-susceptible to Cefiderocol (**CFDC-NS**) over the total number of isolates, according to the respective definition of breakpoints and resistance phenotype. **CFDC-NS**, cefiderocol non-susceptible; **CL**, 95% confidence limit; **PL**, 95% prediction limit; **CAR**, carbapenem; **MBL**, metallo-β-lactamase; **NDM**, New Delhi metallo-β-lactamase; **CZA**, ceftazidime/avibactam; **CTA**, ceftolozane/tazobactam

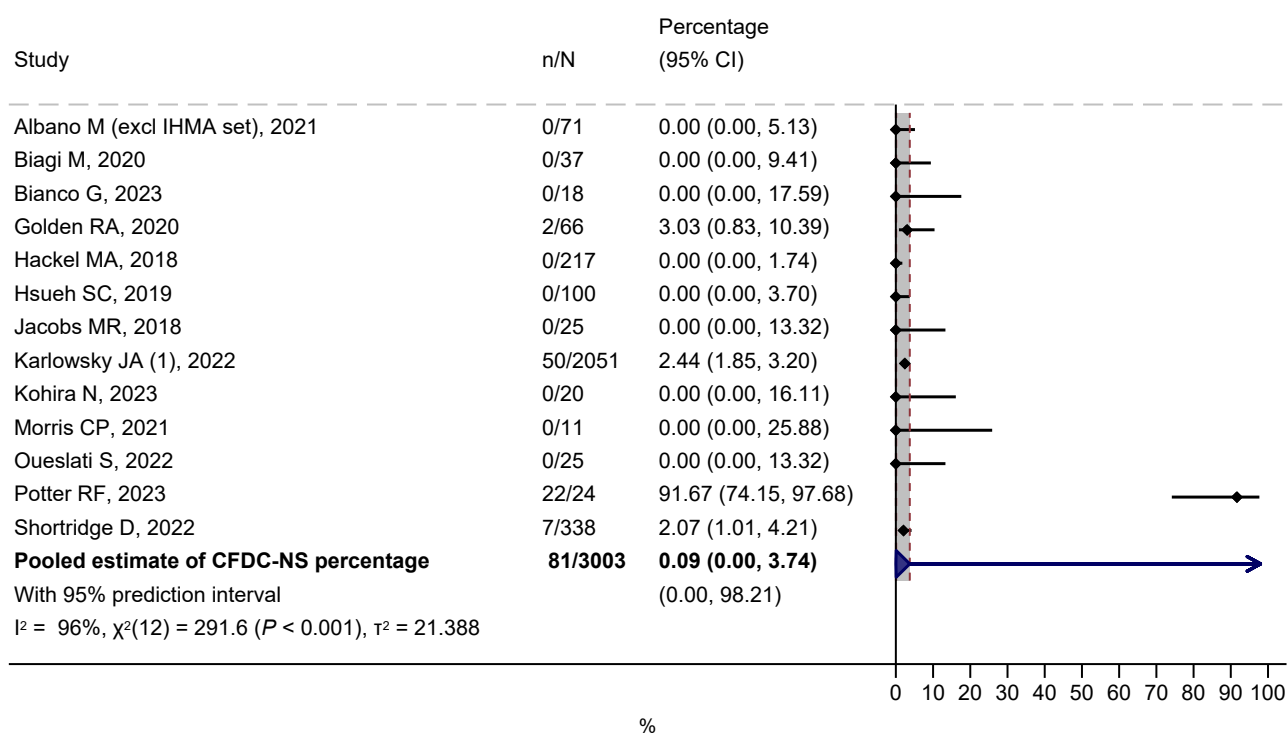
12.2 Forest plots

12.2.1 Previous CLSI breakpoints



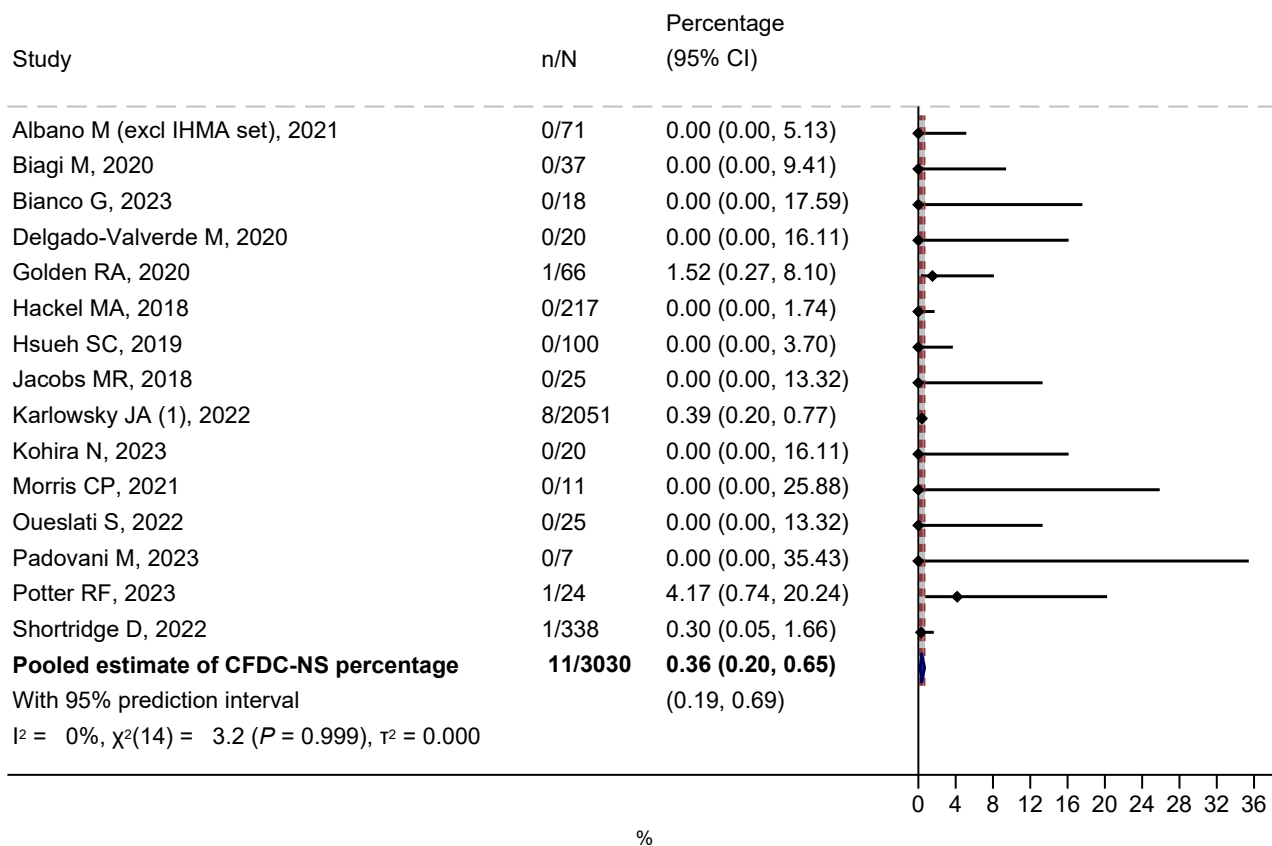
Note. n is the number of *S. maltophilia* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to CLSI old breakpoints. N is the overall number of *S. maltophilia* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

12.2.2 New CLSI breakpoints



Note. n is the number of *S. maltophilia* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to CLSI new breakpoints. N is the overall number of *S. maltophilia* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

12.2.3 EUCAST breakpoints



Note. n is the number of *S. maltophilia* isolates that were non-susceptible to Cefiderocol (CFDC-NS) according to EUCAST breakpoints. N is the overall number of *S. maltophilia* clinical isolates in the study. The diamond's center is the population-averaged percentage (pooled estimate) of CFDC-NS isolates. The diamond's length and the respective grey vertical area indicate the 95% confidence interval of the pooled estimate. The extended line continuing through the confidence interval represents the 95% prediction interval of the percentage of CFDC-NS isolates expected in new studies.

13 Univariate meta-regression analyses

13.1 CR Enterobacterales

Study characteristic	Level	S	Predicted CFDC-NS % (CI)	Odds ratio (CI)	P-value	R ²
Year	2015-2019	5	5.4 (0.0 - 16.3)	Ref.	0.718	0.9%
	2020-2023	31	3.6 (0.5 - 6.7)	0.66 (0.07 - 6.46)		
Region ¹	EUR	12	3.1 (0.0 - 7.2)	0.72 (0.13 - 3.88)	0.700	6.8%
	AMR	8	1.1 (0.0 - 3.3)	0.21 (0.03 - 1.63)	0.136	
	WPR	6	9.6 (0.0 - 26.2)	3.27 (0.40 - 27.02)	0.272	
	Multi-regional	10	6.1 (0.0 - 15.1)	2.05 (0.33 - 12.64)	0.440	
Multinational	No	30	4.1 (0.5 - 7.7)	Ref.	0.662	1.5%
	Yes	6	2.6 (0.0 - 7.7)	0.61 (0.07 - 5.59)		
Multicenter	No	8	27.9 (0.0 - 57.9)	Ref.	0.001	28.1%
	Yes	28	2.2 (0.3 - 4.1)	0.06 (0.01 - 0.33)		
RoB, population and setting	Moderate/High risk	33	4.3 (0.7 - 7.8)	Ref.	0.337	3.1%
	Low risk	3	1.1 (0.0 - 4.1)	0.25 (0.01 - 4.23)		
RoB, condition measurement	Moderate/High risk	19	3.8 (0.0 - 7.9)	Ref.	0.992	0.0%
	Low risk	17	3.8 (0.0 - 8.2)	1.01 (0.20 - 5.06)		

Univariate meta-regression analysis of the associations between study-level characteristics and prevalence of Cefiderocol non-susceptible CR Enterobacterales based on CLSI-FDA breakpoints.

S, the number of independent data sets in the analysis; **CFDC-NS**, Cefiderocol non-susceptible; **CI**, 95% confidence interval; **EUR**, European region; **AMR**, Region of the Americas; **WPR**, Western Pacific Region; **RoB**, risk of bias.

¹ Region defined by the WHO grouping. The odds ratio for each region compares that region to all other regions combined (e.g. EUR vs. elsewhere).

13.2 CR *K. pneumoniae*

Study characteristic	Level	S	Predicted CFDC-NS % (CI)	Odds ratio (CI)	P-value	R ²
Year	2015-2019	4	0.2 (0.0 - 0.8)	Ref.	0.101	13.2%
	2020-2023	19	2.4 (0.1 - 4.8)	11.42 (0.62 - 209.44)		
Region ¹	EUR	8	0.9 (0.0 - 2.3)	0.36 (0.05 - 2.38)	0.287	23.9%
	AMR	5	2.8 (0.0 - 8.3)	1.92 (0.21 - 17.35)	0.560	
	WPR	3	0.5 (0.0 - 1.7)	0.23 (0.02 - 2.93)	0.258	
	Multi-regional	7	4.3 (0.0 - 10.8)	3.77 (0.58 - 24.67)	0.165	
Multinational	No	20	2.0 (0.0 - 3.9)	Ref.	0.384	3.5%
	Yes	3	0.5 (0.0 - 1.9)	0.23 (0.01 - 6.26)		
Multicenter	No	5	4.7 (0.0 - 12.8)	Ref.	0.204	7.5%
	Yes	18	1.3 (0.0 - 2.6)	0.26 (0.03 - 2.08)		
RoB, population and setting	Moderate/High risk	20	1.8 (0.0 - 3.6)	Ref.	0.840	0.6%
	Low risk	3	1.3 (0.0 - 4.6)	0.77 (0.06 - 10.27)		
RoB, condition measurement	Moderate/High risk	13	2.3 (0.0 - 5.1)	Ref.	0.462	4.6%
	Low risk	10	1.2 (0.0 - 2.8)	0.51 (0.08 - 3.09)		

Univariate meta-regression analysis of the associations between study-level characteristics and prevalence of Cefiderocol non-susceptible CR *K. pneumoniae* based on CLSI breakpoints.

S, the number of independent data sets in the analysis; **CFDC-NS**, Cefiderocol non-susceptible; **CI**, 95% confidence interval; **EUR**, European region; **AMR**, Region of the Americas; **WPR**, Western Pacific Region; **RoB**, risk of bias.

¹ Region defined by the WHO grouping. The odds ratio for each region compares that region to all other regions combined (e.g. EUR vs. elsewhere).

13.3 CR *P. aeruginosa*

Study characteristic	Level	S	Predicted CFDC-NS % (CI)	Odds ratio (CI)	P-value	R ²
Year	2015-2019	5	0.6 (0.0 - 1.8)	Ref.	0.739	2.0%
	2020-2023	18	0.9 (0.0 - 1.9)	1.43 (0.17 - 12.01)		
Region ¹	EUR	9	1.1 (0.0 - 2.9)	1.59 (0.26 - 9.60)	0.613	18.8%
	AMR	5	0.5 (0.0 - 1.7)	0.60 (0.06 - 5.99)	0.661	
	WPR	4	0.1 (0.0 - 0.4)	0.07 (0.00 - 1.48)	0.089	
	Multi-regional	5	2.0 (0.0 - 5.2)	3.61 (0.46 - 28.51)	0.223	
Multinational	No	19	1.0 (0.0 - 2.1)	Ref.	0.552	8.4%
	Yes	4	0.5 (0.0 - 1.5)	0.52 (0.06 - 4.41)		
Multicenter	No	5	1.2 (0.0 - 3.4)	Ref.	0.618	0.0%
	Yes	18	0.7 (0.0 - 1.6)	0.59 (0.08 - 4.66)		
RoB, population and setting	Moderate/High risk	22	0.9 (0.0 - 1.8)	Ref.	.	4.5%
	Low risk	1	Insufficient data	Non-estimable		
RoB, condition measurement	Moderate/High risk	8	1.0 (0.0 - 2.5)	Ref.	0.784	1.6%
	Low risk	15	0.8 (0.0 - 1.7)	0.77 (0.12 - 4.87)		

Univariate meta-regression analysis of the associations between study-level characteristics and prevalence of Cefiderocol non-susceptible CR *P. aeruginosa* based on CLSI breakpoints).

S, the number of independent data sets in the analysis; **CFDC-NS**, Cefiderocol non-susceptible; **CI**, 95% confidence interval; **EUR**, European region; **AMR**, Region of the Americas; **WPR**, Western Pacific Region; **RoB**, risk of bias.

¹ Region defined by the WHO grouping. The odds ratio for each region compares that region to all other regions combined (e.g. EUR vs. elsewhere).

13.4 CR *A. baumannii*

Study characteristic	Level	S	Predicted CFDC-NS % (CI)	Odds ratio (CI)	P-value	R ²
Year	2015-2019	4	5.0 (0.0 - 10.2)	Ref.	0.298	4.1%
	2020-2023	22	9.0 (5.2 - 12.8)	1.86 (0.58 - 6.01)		
Region ¹	EUR	9	7.7 (2.0 - 13.4)	0.90 (0.35 - 2.34)	0.836	0.0%
	AMR	6	8.5 (1.6 - 15.5)	1.06 (0.38 - 2.94)	0.907	
	WPR	4	8.2 (0.3 - 16.2)	1.01 (0.32 - 3.18)	0.991	
	Multi-regional	7	8.4 (2.3 - 14.5)	1.04 (0.41 - 2.68)	0.929	
Multinational	No	20	7.6 (4.0 - 11.2)	Ref.	0.556	0.0%
	Yes	6	9.9 (2.5 - 17.4)	1.34 (0.50 - 3.56)		
Multicenter	No	5	18.8 (5.5 - 32.1)	Ref.	0.020	20.6%
	Yes	21	6.7 (3.9 - 9.5)	0.31 (0.12 - 0.83)		
RoB, population and setting	Moderate/High risk	23	7.8 (4.6 - 11.0)	Ref.	0.401	6.3%
	Low risk	3	13.3 (0.0 - 28.6)	1.82 (0.45 - 7.31)		
RoB, condition measurement	Moderate/High risk	10	8.7 (3.2 - 14.2)	Ref.	0.798	0.4%
	Low risk	16	7.9 (3.8 - 11.9)	0.89 (0.37 - 2.15)		

Univariate meta-regression analysis of the associations between study-level characteristics and prevalence of Cefiderocol non-susceptible CR *A. baumannii* based on CLSI breakpoints.

S, the number of independent data sets in the analysis; **CFDC-NS**, Cefiderocol non-susceptible; **CI**, 95% confidence interval; **EUR**, European region; **AMR**, Region of the Americas; **WPR**, Western Pacific Region; **RoB**, risk of bias.

¹ Region defined by the WHO grouping. The odds ratio for each region compares that region to all other regions combined (e.g. EUR vs. elsewhere).

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