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1 **Variable impact of an antimicrobial stewardship programme in three intensive care**
2 **units: time-series analysis of 2012-2017 surveillance data**

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23

24 **Running title**

25 Stewardship in intensive care units

26

27

28 **Synopsis**

29 **Background:** Preprescription authorization (PPA) and postprescription review with feedback
30 (PPRF) were successively implemented in 2012 and 2016 in our 1500-bed hospital.

31 **Aim :** We assessed their impact on carbapenems use and resistance levels of *P. aeruginosa* in
32 three intensive care units (ICU).

33 **Methods:** Carbapenems use (in DDD/1000 occupied bed-days) and resistance of *P.*
34 *aeruginosa* (percentage of non-susceptible (I+R) isolates to imipenem and/or meropenem)
35 were analyzed using a controlled interrupted time-series method. Two periods were
36 compared: 2012-2015 (PPA) and 2016-2017 (PPA+PPRF). Models were adjusted on the
37 annual incidence of extended-spectrum β -lactamase-producing *Enterobacteriaceae*.

38 **Findings:** Carbapenem use was stable over PPA period in all ICUs, with a significant change
39 of slope over PPA+PPRF period only in ICU1 ($\beta_2 = -12.8$, CI=-19.5;-6.1). There was a switch
40 from imipenem to meropenem during PPA period in all three units. Resistances of *P.*
41 *aeruginosa* were stable over the study period in ICU1 and 2, and significantly decreased over
42 PPA+PPRF period in ICU3 ($\beta_2 = -0.18$, CI=-0.3;-0.03).

43 **Conclusion:** In real life conditions and with the same antimicrobial stewardship programme
44 (AMSP) led by a single team, impact of PPRF was heterogeneous between ICUs. Factors
45 driving impact of AMSP should be further assessed in comparable settings through real life
46 data, to target where they could prove cost-effective.

47 **Keywords :** antimicrobial stewardship, carbapenems, *Pseudomonas aeruginosa*, time-
48 series modeling, intensive care unit

49

50 **Introduction**

51 Multidisciplinary antimicrobial stewardship (AMS) programmes have proven effective to
52 decrease mortality, to improve quality of antibiotic prescriptions and to reduce unnecessary
53 antibiotic use [1,2]. Implementation of such programmes is therefore strongly encouraged in
54 all healthcare settings [3,4]. However, when planning implementation of an AMS programme
55 at a hospital scale, prioritizing strategies may be challenging, especially in resource-limited
56 settings. Both restrictive and enabling approaches have been used, and their impact is variable
57 [1,5-7]. In a recent prospective crossover trial [5], a restrictive approach consisting in
58 requirement of pre-prescription approval (PPA), was compared to a post-prescription review
59 with feedback (PPRF) approach. PPRF was more efficient to reduce antibiotic use, suggesting
60 that prioritizing such intervention would have the most significant impact [5]. Conversely,
61 other authors reported an increase of cefepime, piperacillin/tazobactam and vancomycin use
62 when PPA was replaced to PPRF in a prospective non comparative study [6].

63 PPRF requires important human resources that hamper simultaneous implementation in all
64 medical wards of a health-care setting. In most published studies, programmes were either
65 implemented at a hospital scale with substantial dedicated human and financial resources, or
66 restricted to specific departments [8]. There is currently limited evidence on the impact of
67 PPRF at a hospital scale in real-life conditions. In the French context, AMS programmes are
68 primarily supervised by infectious diseases clinicians in addition to their routine clinical tasks,
69 with limited dedicated time to AMS activities [9]. Following national and international
70 recommendations, we implemented in our 1500-bed university hospital a stewardship
71 programme based on PPA and PPRF targeting carbapenem prescriptions. The goal of this
72 study was to assess and compare, in real-life conditions, the impact of PPA and PPRF on
73 antibiotic use and resistance of *Pseudomonas aeruginosa* in three intensive care units (ICU)
74 within a same healthcare setting.

75

76 **Methods**

77 Setting, participants and intervention

78 This retrospective observational study was conducted between 2012 and 2017 in the Hôpitaux
79 Universitaires Paris Centre (HUPC), a 1500-bed university hospital, Paris, France. Patients
80 from three distinct intensive care units were included: ICU1 (24 beds) including patients with
81 severe medical conditions (e.g. severe community-acquired sepsis, out-of-hospital cardiac
82 arrest, etc.), ICU2 (10 beds) post-operative patients after gastrointestinal surgery and ICU3
83 (16 beds) post-operative patients following thoracic surgery. All ICU patients who had
84 received at least one dose of carbapenem (meropenem or imipenem) over the study period
85 were included. The study was conducted in accordance with STROBE-AMS guidelines [10].

86 PPA alone, then PPA + PPRF were successively implemented in 2012 and 2016 in all
87 medical, surgical and intensive care units of the hospital for carbapenem prescriptions. The
88 programme was supervised as part of routine work by the multidisciplinary team available on
89 site, composed of one pharmacist in charge of antibiotics deliveries and of three Infectious
90 Diseases (ID) physicians dedicated to giving daily individual bedside advice for patients with
91 infectious diseases. No additional resources were allocated to implement the AMS
92 programme. Procedures for PPA and PPRF were as reported elsewhere [5,11]. With PPA the
93 prescriber had to seek input from the pharmacists prior to administration of carbapenems. For
94 each carbapenem prescription, the role of the pharmacist was to check whether the indication
95 was concordant with the local guideline, and if not, to discuss alternatives with the clinician in
96 charge. In the second period (PPA+PPRF), in addition to PPA, pharmacists identified new
97 carbapenem prescriptions on a daily basis and sent the list of patients to the ID physicians of
98 the AMS team. In the ensuing 48-72 hours, ID physicians visited the patients, reviewed the
99 clinical charts and interviewed the prescribing physicians during a bedside visit. Based on
100 available diagnostic tests and clinical course, the AMS team advised the clinician with
101 recommendations for stopping, discontinuing, or adjusting therapy. Both ID physicians and

102 pharmacists followed a local guideline derived from national recommendations on treatment
103 durations and promotion of non-carbapenems alternatives [11–13]. The guideline also
104 recommended preferential use of meropenem rather than imipenem based on literature data
105 suggesting better tolerance and greater in vitro activity against Gram-negative pathogens [14].

106

107 Antibiotic use

108 Carbapenem use was estimated from aggregate data of imipenem and meropenem pharmacy
109 deliveries, and expressed as Defined Daily Doses (DDD) per 1000 occupied bed-days (BD).
110 DDD were defined according to ATC/DDD index 2014 [15]. Imipenem and meropenem have
111 the same DDD of 2 grams per 24 hours. However, individual dosing may vary widely
112 between patients, mainly depending on the severity of clinical presentation (typically 1.5g to
113 3g/24 hours for imipenem and 3 to 6 g/24h for meropenem, the highest doses being used in
114 the most critical patients [16]). As previously described, using non-standard doses of
115 antibiotics can affect calculation of DDD [3]. For instance, the highest recommended dose
116 would account for 1.5 DDD for imipenem (3g/24 hours) and 2 DDD for meropenem (6g/24
117 hours), therefore biasing comparisons between molecules. To account for these discrepancies,
118 we randomly selected ten prescriptions of imipenem and meropenem per year and per
119 intensive care unit (n=360 prescriptions) and collected data on individual doses actually
120 prescribed. For each unit, we then calculated a correction coefficient, defined as the mean
121 daily dose of meropenem divided by the mean daily dose of imipenem. Corrected meropenem
122 consumptions were calculated by dividing raw consumptions by the correction coefficient in
123 each unit.

124

125 Antimicrobial resistance

126 Identification of microorganisms used MALDI-TOF and susceptibility testing was performed
127 by disc diffusion methods according to EUCAST guidelines. An isolate was considered non

128 susceptible when tested and interpreted as resistant (R) or with intermediate susceptibility (I)
 129 in accordance with the French and European clinical breakpoint criteria (EUCAST) [17]. Data
 130 were expressed as percentage of resistance (PR), defined as the percentage of non-susceptible
 131 (I+R) isolates, out of all isolates with antimicrobial susceptibility testing. Duplicates from the
 132 same patient were eliminated taking only the first by date of sample collection and isolate
 133 source, and defined as the presence of similar susceptibility patterns for all antibiotics from
 134 the standard list defined by the EUCAST for the species. We first studied the global resistance
 135 to carbapenems, defined as resistance to either imipenem, meropenem, or both. Trends of
 136 individual resistance to one of the two molecules (imipenem or meropenem) were secondly
 137 assessed and are presented in the supplementary material. The incidence of extended-
 138 spectrum β -lactamase-producing *Enterobacteriaceae* (ESBL-E) from all isolates was assessed
 139 per year and per 1000 BD.

140

141 Data analysis

142 Two periods were analyzed: 2012–2015 (PPA alone) and 2016–2017 (both PPA and PPRF).
 143 Analysis of aggregated data was performed through a controlled interrupted time-series
 144 method. The time-series was divided into a pre and post intervention segment. We estimated
 145 the three-monthly consumption of carbapenems with a multiple linear regression model

$$146 \quad consumption_t = \begin{cases} \beta_0 + \beta_1 \times t + \gamma \times Incidence_t^{(ESBL)} & , pre - intervention \\ \beta_0 + (\beta_1 + \beta_2) \times t + \gamma \times Incidence_t^{(ESBL)} & , post - intervention \end{cases}$$

147 In this model, t is a continuous variable indicating the time in trimester since 2012. β_0 is the
 148 intercept which estimates the baseline consumption of carbapenems, β_1 is the change in
 149 consumption during the pre-intervention period, β_2 is the change of slope between the post-
 150 intervention and the pre-intervention period, and γ the parameter associated to the incidence
 151 of ESBL. Since local epidemiology may affect the use of carbapenems, all models were
 152 adjusted on the annual incidence of ESBL-E.

153 We estimated the three-monthly percentage of resistance (PR) of *P. aeruginosa* to
154 carbapenems with a Poisson loglinear regression model:

155 $\log(\text{number of resistant isolates}_t)$

$$156 = \begin{cases} \beta_0 + \beta_1 \times t + \log(\text{number of isolates}) & , \text{pre} - \text{intervention} \\ \beta_0 + (\beta_1 + \beta_2) \times t + \log(\text{number of isolates}) & , \text{post} - \text{intervention} \end{cases}$$

157 Statistical analysis and modeling were performed using the R software (3.3.2) [18].

158 Anonymized routine surveillance data were stored on a secured database regularly declared to
159 the national competent authorities (Commission Nationale Informatique et Libertés). For this
160 type of observational retrospective study, formal consent and permission of an institutional
161 review board are not required.

162

163 **Results**

164 Antibiotic use

165 Over the 3 ICUs, raw consumption of carbapenems was 131 DDD/1000 BD in 2012 and 162
166 DDD/1000 BD in 2017. In the sample of 360 prescriptions, the mean individual dosage was
167 2.5g /24 hours (standard error (SE)=1.0) for imipenem and 5.2g /24 hours (SE=1.5) for
168 meropenem, leading to a correction coefficient of 2. The interrupted time-series showed no
169 change in overall corrected carbapenem use during the PPA period ($\beta_1=+0.1$, 95% confidence
170 interval (CI)= -13.1;+13.3), and no change of slope over the PPA+PPRF period ($\beta_2=-3.3$, CI=
171 -9.4;+2.8). There was however a switch between imipenem and meropenem: while overall
172 consumption of imipenem steadily decreased, meropenem increased over the PPA period in
173 all three units (tables S1 and S3, supplementary material).

174 Within each ICU, carbapenem use showed different patterns. In ICU 1, carbapenem use was
175 stable over the PPA period, along with a progressive replacement of imipenem by meropenem
176 (Figure 1). After implementation of PPRF, overall carbapenem consumption significantly
177 dropped, related to a change of slope for both imipenem ($\beta_2=-7.57$, CI = -12.69; -2.45, table
178 1) and, to a lesser extent, meropenem use ($\beta_2=-11.39$ CI = -25.23; +2.46, table 1). In ICU 2

179 and ICU 3, a switch from imipenem to meropenem also occurred during the PPA period, but
180 we observed no impact of PPRF neither on overall consumption, nor imipenem and
181 meropenem use.

182 As shown in table 1, in all units, the annual incidence of ESBL-E was not statistically
183 associated with carbapenem use.

184

185 Antimicrobial resistance

186 The overall PR of *P. aeruginosa* to carbapenems in the three ICUs was of 40% in 2012 and
187 35% in 2017 (imipenem : 33% in 2012, 27% in 2017; meropenem : 23% in 2012, 24% in
188 2017).

189 Global resistance of *P. aeruginosa* to carbapenems (imipenem and/or meropenem) was stable
190 during the PPA period, with no significant change after implementation of PPRF over the
191 three units (figure 2, table 2). Similar patterns were observed in ICU 1 and ICU 2. In ICU 3, a
192 significant decrease in global resistance was observed in the PPA+PPRF period, related to a
193 decrease of imipenem resistance ($\beta_2=-0.19$, CI=-0.4;-0.01, table S2), whereas meropenem
194 resistance remained stable ($\beta_2=-0.06$, CI=-0.26;+0.15, table S4).

195

196 **Discussion**

197 In this retrospective study based on surveillance data, we report heterogeneous impact of an
198 AMS programme within three ICUs of the same hospital. Carbapenem use did not change
199 over the PPA period in all three ICUs, and significantly decreased in only one ICU after
200 implementation of PPRF. A switch from imipenem to meropenem was observed in the three
201 ICUs during the PPA period. Resistance rates showed similar patterns and were stable over
202 the study period within the three units.

203

204 As previously reported, PPA alone had a limited impact on the overall carbapenem use in our
205 setting, apart from a switch from imipenem to meropenem use. This switch during the study
206 period was probably related to adherence to local guidelines, actively promoted by the
207 pharmacists and ID physicians of the AMS team [14]. In the trial by Tamma et al., antibiotic
208 consumptions remained steady during PPA periods in both arms [5]. A Cochrane review and
209 meta-analysis confirmed that restrictive strategies were less effective than enabling
210 interventions with feedback to enhance compliance to antibiotic strategies [1]. Moreover,
211 several studies revealed unintended consequences of PPA: negative professional culture
212 through breakdown in trust and communication [19,20] and delay in time to first antibiotic
213 dose [21] . In practice, there are many barriers for implementation of PPA in a healthcare
214 setting. PPA requires someone to be available to answer requests in real time, 24/7. Antibiotic
215 approval practices may also differ between stewardship practitioners depending on their
216 background, level of experience [11] . In many health-care settings, pharmacists are dedicated
217 to this task. However, even if extensively trained on antibiotic stewardship, most pharmacists
218 feel to have limited capacity to influence antibiotic decision-making, mainly due to the
219 perception of antibiotic use as a medical responsibility [22] . This is particularly true in ICUs
220 where patients are critically unwell, at high risk for carriage of multidrug-resistant bacteria,
221 and where physicians are highly experienced in prescribing antibiotics. All these limitations
222 raise concerns on effectiveness of PPA in practice and even more of its medico-economic
223 impact.

224

225 PPRF showed encouraging positive effects [5,7,23] , leading to its positioning as a
226 cornerstone of AMS programmes [24] . In our study, PPRF showed a significant impact on
227 carbapenem consumption in one out of three ICU units. In comparison, Abbara et al. reported
228 in a single ICU a decrease in broad spectrum antibiotics use – among which carbapenems –
229 and resistance of *P. aeruginosa* after a strategy combining: i) systematic PPRF of all

230 antibiotics, ii) restriction of broad spectrum antibiotics through local guidelines. While our
231 AMS programme targeted only carbapenems in the whole hospital, their AMS programme
232 targeted all broad-spectrum antibiotics in a single ICU. Like PPA, PPRF is a resource-
233 consuming strategy since members of the AMS team must be available on site to review
234 prescriptions within 24-48 hours. Thus, focusing the AMS programme on a single ICU could
235 partly explain their different results. Second, effectiveness of the strategy highly depends on
236 adherence of the caring physicians to recommendations of the AMS team [24,25]. Factors that
237 drive adherence to ID advices are not fully understood. Several reports underlined that the
238 strongest drivers were stewards and prescribers' behavior and beliefs, rather than patients'
239 characteristics [24-26]. Recent qualitative work investigated that issue, putting forward
240 factors such as local culture and practices, physicians' personal experiences, involvement of
241 supra-level bodies like hospital authorities, physician's interest and willingness to conform to
242 guidelines, competition between physicians and AMS team's qualifications and tasks, lack of
243 interaction between the AMS team and senior doctors while care delivery is very
244 hierarchically structured [26-28]. Because these factors are very heterogeneous, it is difficult
245 to anticipate in which setting PPRF is likely to have the highest impact.

246

247 Our results on antibiotic resistance were deceiving, despite a marginal decrease of imipenem
248 resistance during the PPA+PPRF period in a single ICU. The number of *P.aeruginosa* isolates
249 in this ICU was low which could account for a high variability of results. Moreover, this was
250 observed in only one ICU, while imipenem consumption had been previously decreasing for
251 several years in all three ICUs. If the switch from imipenem to meropenem had an impact on
252 *P.aeruginosa* resistance to imipenem, we would have assumed to see a sustainable and similar
253 effect in the three ICUs, which we did not observe.

254 Several studies suggest a strong correlation between carbapenem use and the proportion of
255 carbapenem-resistant *P. aeruginosa* isolates, particularly in settings where chromosomally

256 encoded resistance mechanisms (loss of OprD porin, overproduction of the MexAB efflux
257 system) are predominant, like in France. For instance, in a retrospective study in a French
258 ICU [29], imipenem resistance of *P. aeruginosa* strains was mainly due to chromosomally
259 encoded resistance mechanisms, and the main risk factor for resistance was prior exposure to
260 imipenem (Odds ratio = 6.8 [95% CI, 1.2 to 50.2] when patients received > 3 days of
261 imipenem). The correlation between antibiotic use and emergence of resistance is not
262 straightforward for other Gram-negative bacteria (i.e. resistance to 3GC and ESBL-
263 *Enterobacteriaceae*), explaining why we specifically chose to focus on the pairing of “*P.*
264 *aeruginosa* / carbapenems” to evaluate the impact of the programme.

265 Failure to show any impact of our strategies on carbapenems resistance could be due to a real
266 lack of effect, to confounding factors, or a too short period of observation after
267 implementation of PPRF (2 years). The effect of AMS programmes on antibiotic resistance, in
268 particular of *P. aeruginosa*, remains unclear and inconsistent between studies [1, 30, 31].
269 Actual evidence shows too much variance in microbial outcomes to reliably assess the effect
270 of change in antibiotic use on gram-negative bacteria and to discriminate the impact of each
271 strategy [31].

272

273 This study has several limitations. As it is an uncontrolled study, PPA and PPRF occurred in
274 two different periods, during which other changes could have impacted antibiotic prescribing
275 practices. Because carbapenems are mainly used in the treatment of ESBL-E infections, we
276 adjusted our models on the incidence of ESBL-E isolates from each unit. However, in all
277 models, the parameter was not statistically significant, meaning that the ESBL-E incidence
278 had no significant impact on carbapenem consumption over the study period. Still, other
279 factors impacting bacterial resistance were not assessed, as fluoroquinolones’ cross-over
280 impact on carbapenem resistance, clinical characteristics of the patients, iatrogenic factors
281 (use of invasive devices, mechanical ventilation, etc.) [32-34]. Another limitation is that we

282 did not assess adherence to PPRF, while it is a major success factor in non-coercive strategies
283 [22,24]. Finally, there was a high variability over time in carbapenem consumption on a
284 microscale level in each ICU. Because we reported antibiotic deliveries and not antibiotic use,
285 this may be explained by stockpiling in the three units.

286

287 Until now, most published studies analyzed the effect of AMS strategies in a single setting,
288 while we compared the effect of one strategy led by the same AMS team in three different
289 settings from the same hospital [30]. Analyzing impact at hospital level increases statistical
290 power, but can also hide differential impacts within different medical units. Our study reports
291 observational surveillance data, offering the opportunity to observe real-life effects of PPA
292 and PPA+PPRF. In this pragmatic approach, our goal was to observe whether any trend
293 would be observed after implementation of the programme, and to compare different settings.
294 This approach does not allow to formally relate a change in resistance to a change in
295 antibiotic use. However, our data show that in real-life conditions, when implementing an
296 AMS program, variable impact may be observed depending on the setting, within the same
297 hospital. Taking that variability into account is important for deciding how to effectively split
298 resources allocated to AMS programmes.

299

300

301 **Conclusion:** In real life conditions, after implementation of an AMS programme based on
302 systematic post-prescription review of all carbapenem prescriptions, we report a decrease of
303 antibiotic use in only one out of three ICUs, with no clear impact on carbapenem resistance of
304 *P. aeruginosa*. This suggests that within the same hospital, systematic post-prescription
305 review by an antibiotic expert may have a heterogeneous impact from a unit to another. Due

306 to financial and organizational constraints, such an approach should be prioritized in specific
307 wards and predictors of successful implementation still need to be assessed.

308

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314

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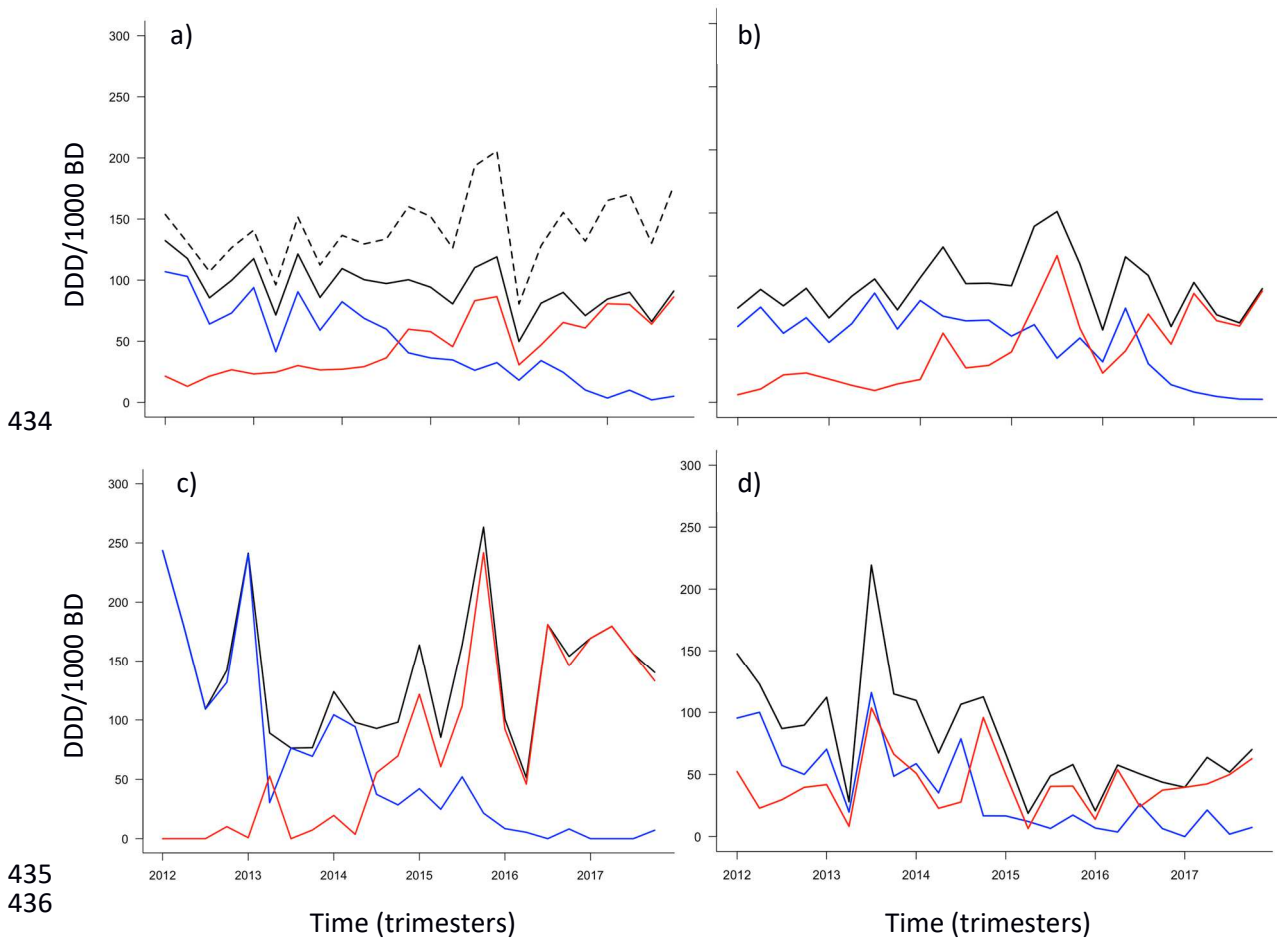
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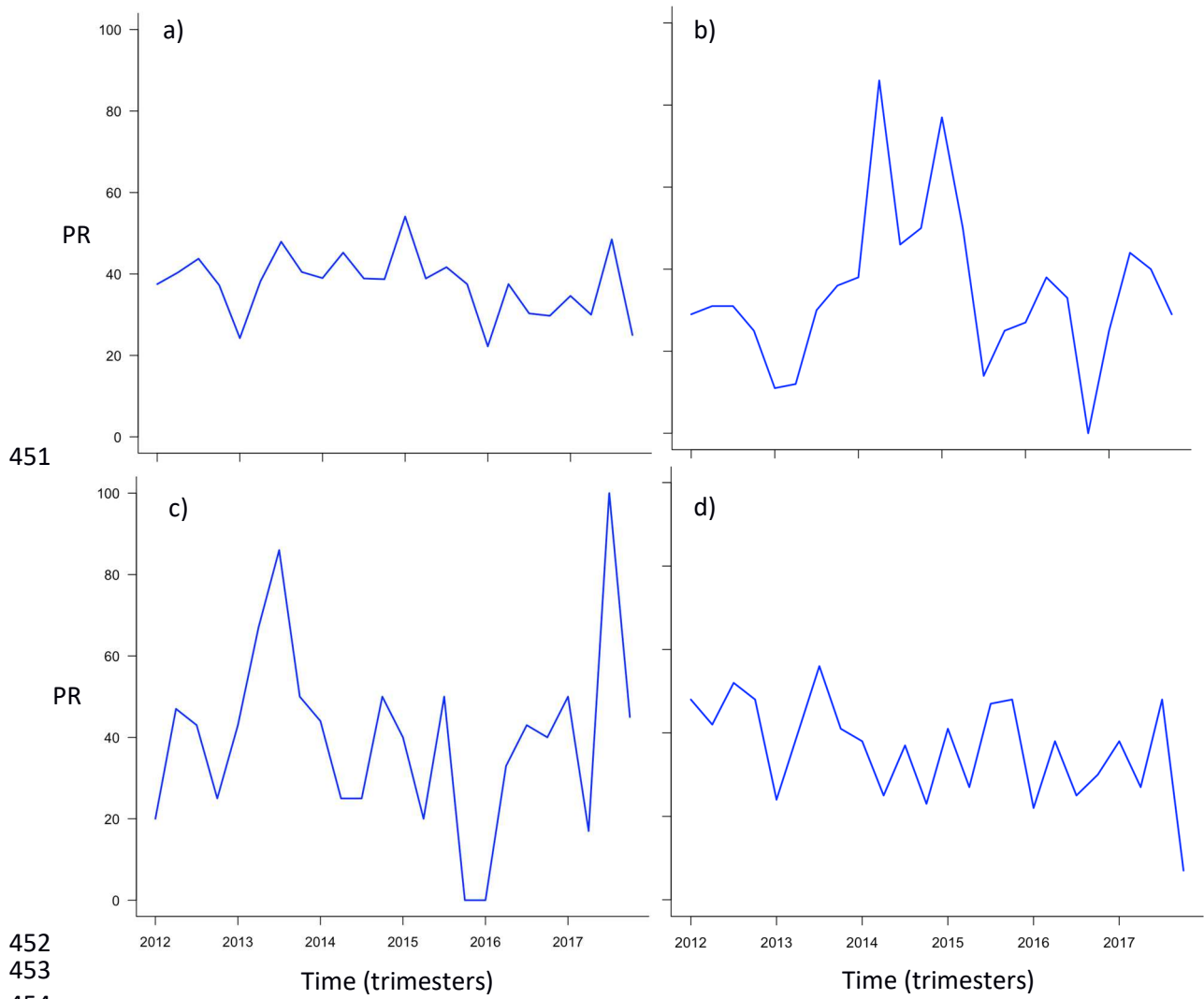
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432

433 **Figure 1.**



450 **Figure 2.**



476 **Tables**

477

478 **Table 1.** Parameters of the multiple linear regression models for corrected carbapenem use

| | Intercept β_0 [CI] | PPA period | | PPA+PPRF period | | Incidence ^(ESBL) | |
|------|-----------------------------|-----------------------|---------|-----------------------|-------------------|-----------------------------|---------|
| | | β_1 [CI] | P-value | β_2 [CI] | P-value | ν [CI] | P-value |
| All | 76.6 [-88.6;+241.8] | 0.1 [-13.1;+13.3] | 0.99 | -3.3 [-9.4;+2.8] | 0.27 | 8.4 [-39.4;+56.2] | 0.72 |
| ICU1 | 147.3 [-34.4;+328.9] | 8.8 [-5.8;+23.3] | 0.22 | -12.8 [-19.5;-6.1] | <10 ⁻³ | -22.0 [-74.5;+30.6] | 0.39 |
| ICU2 | 3.9 [-572.1;+579.9] | 6.1 [-40.1;+52.3] | 0.79 | 4.7 [-16.6;+25.9] | 0.65 | 41.0 [-125.7;+207.6] | 0.61 |
| ICU3 | -46.2 [-417.3;+324.9] | -6.7 [-36.5;+23.0] | 0.64 | 4.7 [-9.0;+18.4] | 0.48 | 50.4 [-56.9;+157.7] | 0.34 |

479

480 *Abbreviations:* CI : 95% confidence interval; ESBL : extended-spectrum β -lactamase-
481 producing *Enterobacteriaceae*.

482

483

484 **Table 2.** Parameters of the multiple linear regression models for the proportion of resistance
485 to carbapenems of *P. aeruginosa*

| | Intercept β_0 [CI] | PPA period | | PPA+PPRF period | |
|----------|-----------------------------|--------------------|---------|--------------------|---------|
| | | β_1 [CI] | p-value | β_2 [CI] | p-value |
| All ICUs | -1.0 [-1.2;-0.8] | +0.03 [-0.06;+0.1] | 0.45 | -0.07 [-0.2;+0.01] | 0.08 |
| ICU1 | -0.8 [-1.1;-0.5] | -0.05 [-0.2;+0.1] | 0.47 | -0.02 [-0.1;+0.1] | 0.71 |
| ICU2 | -0.8 [-1.3;-0.3] | -0.02 [-0.3;+0.2] | 0.85 | -0.01 [-0.2;+0.2] | 0.96 |
| ICU3 | -1.35 [-1.8;-0.9] | +0.23 [+0.04;+0.4] | 0.02 | -0.18 [-0.3;-0.03] | 0.01 |

486

487 *Abbreviations:* CI : 95% confidence interval; ESBL : extended-spectrum β -lactamase-
488 producing *Enterobacteriaceae*.

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501 **Figure captions**

502

503 **Figure 1: Carbapenem use in DDD/1000 BD over time**

504 **This figure is online-only color**

505 a) in all ICUs, b) in ICU 1, c) in ICU 2, d) in ICU 3

506 Black dotted line: raw carbapenem consumption (imipenem+meropenem).

507 Black line: corrected carbapenem consumption (imipenem+meropenem).

508 Blue line: imipenem consumption.

509 Red line: corrected meropenem consumption.

510 Overall incidence of ESBL in all ICUs, from 2012 to 2017, per 1000 occupied bed-days :

511 3.34, 3.34, 2.71, 2.71, 2.13, 2.11

512

513 **Figure 2: Proportion of resistance to imipenem and/or meropenem in *Pseudomonas***
514 ***aeruginosa* isolates over time**

515 **This figure is online-only color**

516 a) in all ICUs, b) in ICU 1, c) in ICU 2, d) in ICU 3

517 Total number of isolates per year, from 2012 to 2017 : ICU 1 [34/27/23/30/20/19], ICU 2

518 [12/12/14/5/8/7], ICU 3 [15/11/24/21/8/7]

519