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1 **An investigation of the effects of procalcitonin testing on antimicrobial prescribing in respiratory**
2 **tract infections in an Irish University Hospital setting - a feasibility study.**

3

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12 **Synopsis**

13 Diagnostic uncertainty and a high prevalence of viral infections present unique challenges for
14 antimicrobial prescribing for respiratory tract infections (RTIs). Procalcitonin (PCT) has been
15 shown to support prescribing decisions and reduce antimicrobial use safely in patients with RTIs but
16 recent study results have been variable.

17 **Methods**

18 We conducted a feasibility study of the introduction of PCT testing in patients admitted to hospital
19 with a lower RTI to determine if PCT testing is an effective and worthwhile intervention to introduce
20 to support the existing AMS programme and safely decrease antimicrobial prescribing in patients
21 admitted with RTIs.

22 **Results**

23 A total of 79 patients were randomised to the intervention PCT guided treatment group and 40
24 patients to the standard care respiratory control group.

25 The addition of PCT testing led to a significant decrease in duration of antimicrobial
26 prescriptions (mean 6.8 versus 8.9 days $p=0.012$) and decreased length of hospital stay (median
27 7 versus 8 days, $p=0.009$) between the PCT and respiratory control group. PCT did not demonstrate
28 a significant reduction in antimicrobial consumption when measured as DDDs and days of
29 therapy.

30 **Conclusions**

31 PCT testing had a positive effect on antimicrobial prescribing during this feasibility study. The
32 successful implementation of PCT testing in a randomised controlled trial requires an ongoing
33 comprehensive education programme, greater integration into the AMS programme and delivery of
34 PCT results in a timely manner. This feasibility study has shown that a larger randomised controlled
35 trial would be beneficial to further explore the positive aspects of these findings.

36

37 **Introduction**

38 Antimicrobial resistance (AMR) is a major risk to public health globally that leads to increasing
39 healthcare costs, treatment failure, and increased morbidity and mortality.¹⁻³ There is a strong
40 association between sub-optimal antimicrobial prescribing and AMR.⁴ To optimise prescribing,
41 hospital antimicrobial stewardship (AMS) programmes should target areas of high antimicrobial
42 prescribing. One such area is respiratory tract infections (RTIs). Shorter antimicrobial courses offer one
43 potential solution to the overuse of antimicrobials for RTIs⁵ and there is evidence to support such
44 strategies^{6,7} even in severe hospital infections.⁸

45 Diagnostic uncertainty and a high prevalence of viral infections present unique challenges for
46 antimicrobial prescribing for RTIs.⁹⁻¹² This contributes to over-use and/or sub-optimal use of
47 antimicrobials^{13, 14} for RTIs such as community acquired pneumonia (CAP), including prolonged
48 treatment courses of up to 11 days,¹⁵ without a correlation between duration of treatment and
49 infection severity.^{15,16} Physicians are often reluctant to shorten antimicrobial course durations due to
50 the fear of incomplete pathogen eradication which could potentially lead to relapse and associated
51 morbidity and mortality.⁶ There is also a high rate of antimicrobial continuation where viral
52 infections,¹⁷ including influenza,¹⁸ are identified due to overriding concerns about secondary bacterial
53 infections. However, a recent study has shown a bacterial co-infection rate of only 40%.¹¹

54 To address these issues, there is a growing interest in the use of novel diagnostic techniques and
55 biomarkers as an AMS tool.¹⁹ It is important that AMS programmes investigate the opportunity
56 afforded by these new techniques and the potential they offer to optimise antimicrobial treatment
57 more promptly²⁰ and change prescribing behaviour.²¹ Procalcitonin (PCT) testing is one such diagnostic
58 technique. PCT is a peptide precursor to the hormone calcitonin. It is usually undetected but is
59 upregulated in response to a bacterial infection following stimulation of bacterial-induced cytokines.²²
60 Upregulation of PCT is blocked in viral infections due to the release of the cytokine interferon gamma,
61 resulting in a higher specificity of PCT to distinguish between bacterial and viral infections when
62 compared to other inflammatory markers such as CRP.²³ PCT levels decrease rapidly when patients

63 are recovering from infection.²⁴ Hence it offers the potential to support clinical decision making for
64 the initiation and discontinuation of antimicrobials in patients with a clinical suspicion of a bacterial
65 infection when considered along with the clinical assessment of the patients. PCT has been shown to
66 support prescribing decisions and reduce antimicrobial use safely in patients with RTIs²⁵⁻²⁸ but findings
67 from recent studies have been variable,^{29 30} so it is unclear if it is an effective intervention as part of
68 an AMS programme.

69 The purpose of this study was to conduct a feasibility study to determine if PCT testing is an effective
70 and worthwhile intervention to introduce in a University Teaching Hospital to support the existing
71 AMS programme and safely decrease antimicrobial prescribing in patients admitted with RTIs.

72

73 **Methods**

74 We conducted a single centre, randomised, open-label feasibility study of the introduction of PCT
75 testing in patients admitted to hospital with a lower RTI under the care of the respiratory medicine
76 team during on-call acute unselected general medical take to determine if PCT testing had an impact
77 on antimicrobial consumption and patient's length of stay (LOS) in hospital. The study was conducted
78 in a single 321 bed inner city, voluntary acute University Teaching Hospital, which is part of the
79 South/South West Hospital Group³¹ in the Republic of Ireland. It is a Model 3 (smaller general) ³²
80 hospital with a 24-hour emergency department, ICU and admits undifferentiated acute medical and
81 surgical patients. The hospital has an established AMS programme and no significant changes were
82 made to the AMS policies or programme during this study.

83 **Ethics**

84 The study was approved by the local ethics committee (approval code ECM 4 (w) and ECM 3 (III)).
85 Written informed consent was obtained from all participants prior to study enrolment.

86 **Education and training**

87 The microbiology laboratory scientists received technical advice and training on the operation of the
88 PCT assay from the manufacturer prior to study commencement. They also received a presentation
89 on the introduction of PCT testing in the hospital.

90 The respiratory medicine team received presentations at the respiratory journal club meetings and
91 provision of written materials electronically. Presentations consisted of evidence supporting PCT use
92 in practice, limitations of PCT testing, PCT measurement, and interpretation using a PCT-based
93 antimicrobial prescribing algorithm (Supplementary material S1). Presentations were given prior to
94 the study commencement and following medical staff rotation changes. The study protocol
95 (Supplementary material S2), study flow chart and the PCT-based antimicrobial prescribing algorithm
96 was provided to all physicians electronically.

97 **Recruitment and consent**

98 ***Inclusion criteria***

99 Adult patients ≥ 18 years of age, admitted to hospital under the care of the respiratory teams with an
100 initial diagnosis of an acute lower RTI (i.e. Community acquired pneumonia³³ with severity defined by
101 CURB-65 score³⁴, Lower RTIs³⁵, exacerbation of asthma³⁶, COPD³⁷, bronchiectasis³⁸, interstitial lung
102 disease³⁹ and influenza³⁵) and commenced on antimicrobial therapy were identified from the daily
103 admission census or by the respiratory medicine teams.

104 The randomisation process stratified patients according to presence or absence of severe COPD GOLD
105 Stage D criteria 2017³⁷ to ensure balanced treatment allocation. Patients were then randomly
106 allocated in a 2:1 ratio to either the PCT guided treatment group or the standard care respiratory
107 control group. Randomisation was carried out using sequentially numbered opaque sealed envelopes.
108 A second general control group of patients admitted under general medicine teams with a diagnosed
109 acute lower RTI and received standard care (no PCT measurement) was recruited to provide a
110 comparison of antimicrobial prescribing in RTIs by non-respiratory specialist physicians in the hospital.

111 **Exclusion Criteria**

112 Exclusion criteria were: unable to give written informed consent due to language restrictions,
113 cognitive impairment or severe dementia; re-admission to hospital within 30 days of previous
114 admission; immunosuppression (neutropenic, chemotherapy, radiation therapy or
115 immunosuppressive therapy) other than corticosteroid use; life-threatening medical co-morbidities
116 leading to possible imminent death, Do Not Resuscitate (DNR) status; patients with concurrent chronic
117 infections necessitating prolonged antimicrobial treatment (cystic fibrosis, tuberculosis, infective
118 endocarditis, osteo-articular infections, hepatic or cerebral abscesses, chronic prostatitis); patients
119 with >24 hours of appropriate antimicrobial therapy prior to initial PCT level; active intravenous drug
120 users; pregnant women.

121 **Intervention**

122 PCT testing was commenced in the microbiology department following completion of staff training
123 and instrument validation. It was available during routine working hours (Monday to Friday, 9am-
124 5pm). PCT serum concentrations were measured using the VIDAS BRAHMS PCT (assay range 0.05-200
125 µg/L) (Biomerieux, France).

126 PCT serum concentrations were interpreted using an evidence based algorithm (Supplementary
127 material S1)⁴⁰ which has been validated in previous studies^{28 29} recommending antimicrobials strongly
128 discouraged for PCT levels < 0.1 µg per litre, discouraged for levels 0.1 to 0.25 µg/L, encouraged for
129 levels > 0.25 to 0.5 µg/L and strongly encouraged for levels > 0.5 µg/L. The algorithm also included
130 specific overruling criteria where antimicrobials could be considered in the case of respiratory or
131 haemodynamic instability; life-threatening co-morbidity; need for ICU admission; PCT < 0.1 µg /mL:
132 CAP with CURB 65 > 3, COPD stage IV; PCT < 0.25 µg/mL: CAP with CURB 65 > 2; localised infection
133 (abscess, empyema); immunocompromised (other than corticosteroids); concomitant infection in
134 need of antimicrobials.

135 The antimicrobial prescribing advice generated from the PCT algorithm was verbally communicated
136 to the respiratory medicine team and this advice was non-binding. The respiratory medicine team
137 retained prescribing autonomy regarding clinical decisions irrespective of the PCT level or algorithm
138 generated antimicrobial prescribing advice. The algorithm adherence for antimicrobial prescribing
139 recommendations was recorded at 24 hours following the PCT test for all patients along with the
140 rational for prescribing decisions. Algorithm adherence was defined as antimicrobial therapy that was
141 continued or discontinued in accordance with the PCT cut-off ranges. Non-adherence was defined as
142 antimicrobial therapy that was not discontinued despite low PCT levels. Over-riding criteria were not
143 considered when measuring adherence but were recorded as reasons for non-adherence.

144 Patients were followed until their discharge. A further follow up of medical records took place at 30
145 days post admission to identify re-admitted patients and re-admitted patients with infection re-lapse.

146 Patient recruitment ran from June 1st 2017 to May 31st 2018. Figure 1 represents the patient hospital
147 journey with a respiratory tract infection.

148 **Outcomes**

149 The primary outcomes were to quantify the individual inpatient antimicrobial consumption,
150 prescription duration and the inpatient LOS. Following a recent systematic review which
151 recommended that antimicrobial use should be expressed in at least two metrics simultaneously,⁴¹
152 antimicrobial consumption was measured using DDDs, days of therapy (DOTs) and prescription
153 duration. DDDs were calculated using the Anatomical Therapeutic Chemical/Defined Daily Dose
154 (ATC/DDD) index of the WHO Collaborating Centre for Drug Statistics Methodology⁴² but were not
155 adjusted for hospital activity. Days Of Therapy (DOT)⁴³ calculates individual patient-days of
156 antimicrobial exposure and accounts for dosing and frequency of each drug. Antimicrobial prescription
157 duration was measured in days (defined as the number of days between the commencement and
158 discontinuation of antimicrobials). The LOS was defined as date of discharge less date of admission.

159 Secondary outcomes were number of infection and antimicrobial related adverse events during in-
160 patient LOS including mortality, hospital re-admission, and infection re-lapse requiring re-admission
161 both within 30 days. Algorithm adherence for antimicrobial prescribing recommendations was
162 measured.

163 A qualitative process evaluation of the study was conducted in parallel with this feasibility study and
164 will be reported in a subsequent paper.

165 ***Statistical methods***

166 A Microsoft Access database (version 1903) was developed to record the study data. Statistical
167 analysis was conducted using R (version 3.4.0) and was conducted on an intention to treat basis.

168 The primary outcome of antimicrobial consumption between the PCT and respiratory control arms
169 was evaluated using the non-parametric Wilcoxon Rank Sum test. A Kaplan-Meier curve was used to
170 analyse the median time to discharge between the PCT and respiratory control group.

171 Chi-square tests were used to evaluate differences between the PCT and respiratory control arms for
172 all secondary outcomes - number of adverse events, re-admission and infection re-lapse requiring re-
173 admission both within 30 days.

174

175 **Results**

176 The respiratory medical teams admitted 823 general medical patients of whom 313 patients were
177 classified as a respiratory infection or respiratory disorder during the recruitment period of June 1st
178 2017 to May 31st 2018. A CONSORT flow diagram of recruitment can be seen in figure 2.

179 A further 48 patients were recruited to the general control group. Three patients who were identified
180 as suitable to enter the general control group were not recruited due to confusion, isolation due to
181 infection and refused consent.

182 Demographic data and study overview are contained in Table 1. Clinical findings of patients on
183 admission to hospital are contained in Table 2.

184 There were several differences between the baseline characteristics of the PCT group and respiratory
185 control group. The PCT group contained more male patients (60% versus 42%), active smokers (25%
186 versus 12.5%) and patients with pre-existing COPD A-C (29% versus 17%).

187 There were a number of differences in final diagnosis between the PCT group and the respiratory
188 control group with asthma (3.8% versus 15%), CAP (10% versus 7.5%), LRTI (30.4% versus 17.5%. CAP
189 severity in the PCT group had CURB-65 scores ranging from 0 to 3 with a mean of 1.87 while the CAP
190 severity in the respiratory control group had CURB-65 scores ranging from 0 to 1 with a mean of 0.66.

191 The clinical findings on admission were similar between group with two exceptions where the PCT
192 group had a higher percentage of patients who were productive of sputum on admission (49% versus
193 37%) and patients prescribed antibiotics prior to admission (35% versus 25%).

194 **Procalcitonin testing and results**

195 The 79 patients randomised to the PCT group had a total of 163 PCT levels taken (median of 2 tests
196 per patient (range 1-6). Overall the PCT levels had a median of 0.075µg/L (IQR 0.05 – 0.26). The initial
197 PCT level was ≤0.24 µg/L for 58 patients (including 38 patients with an initial PCT level of ≤0.05 µg/L).
198 Our primary outcome was to determine the inpatient antimicrobial consumption, duration of
199 antimicrobial treatment and hospital LOS. The main outcomes can be seen in Table 3 and Figure 3.
200 Statistical analysis was conducted on the PCT and respiratory control groups and does not include
201 comparison with the general control group.

202 There was no significant difference in antimicrobial exposure or usage per patient when measured
203 as DDD (11.1 ± 7.5 versus 13.1 ± 10.7 , $p=0.218$) (mean \pm SD) or DOT (8.9 ± 6.3 versus 11 ± 7.6 ,
204 $p=0.077$) of patients between the PCT and respiratory control group. Median values of both metrics
205 DDD (8.66 versus 9.57) and DOT (7.5 versus 8.25) showed a decrease of 9% in antimicrobial
206 consumption per patient.

207 There was a significant difference in the antimicrobial duration in days between the PCT and
208 respiratory control groups (median 7 versus 8 days, $p=0.0125$). There was also a significant
209 difference between the PCT and respiratory control groups in the median LOS ($p=0.009$) and this can
210 also be seen in the Kaplan–Meier curves in Figure 4.

211 In the analysis of secondary outcomes there was no significant differences between the PCT and
212 respiratory control groups in the incidence of adverse events during in-patient hospital stay
213 ($p=0.9852$), the rate of hospital re-admission ($p=0.1507$), and the rate of infection re-lapse requiring
214 re-admission both within 30 days ($p=0.0924$).

215 Algorithm compliance is displayed in table 4.

216 Overall PCT algorithm compliance per patient was 35% within 24 hours of PCT level being taken. 25
217 patients had high PCT levels (≥ 0.25 µg/L) where the algorithm recommendation was to continue

218 antimicrobial treatment and algorithm compliance was 100%. 67 patients had low PCT levels (< 0.25
219 µg/L) where the algorithm recommendation was to discontinue antimicrobial treatment and
220 algorithm compliance was low (10%). In these instances, the reasons for non-adherence were based
221 on a clinical decision in 55/112 (49%) PCT levels with the remaining 57/112 (51%) PCT levels based on
222 meeting various algorithm overriding criteria (respiratory or haemodynamic instability; life
223 threatening co-morbidity; need for ICU admission; localised infection (abscess, empyema)).

224 Seven patients had their antimicrobial treatment discontinued in compliance with the algorithm when
225 PCT levels were low (< 0.25 µg/L). This resulted in shorter course lengths in five patients (< 7 days) 1
226 course length completion as planned at 7 days, and early antimicrobial discontinuation (day 2) in a
227 patient with influenzae. There were no hospital readmissions among these patients.

228 In a further 9 patients where there was initial non-compliance with the algorithm recommendations
229 when measured at 24 hours, their antimicrobial treatment was subsequently modified resulting in a
230 shorter course length in 7 patients (< 7 days) and 2 further patients discontinued antimicrobials prior
231 to discharge (1 patient re-admitted with infection).

232 Algorithm compliance by indication was as follows; CAP (80%), asthma (50%) LRTI (30%), COPD (12.5%)
233 and influenza virus (42%). PCT levels and algorithm compliance were found to be low in patients with
234 COPD stage D and structural lung conditions like bronchiectasis and interstitial lung disease. In these
235 cases, the clinical judgement of physicians was to over-ride the algorithm recommendations and
236 continue antimicrobials.

237 **Microbiology positive specimens**

238 38 patients (23%) had positive microbiology results : 13 influenzae virus, 10 bacterial isolates from
239 respiratory specimens and 7 yeast isolates from respiratory specimens.

240 **Adverse events**

241 Infection and antimicrobial related adverse events included gastro-intestinal (antimicrobial related
242 diarrhoea 1 patient) renal function (acute kidney injury secondary to antimicrobials 1 patient), liver
243 function (increased liver function tests secondary to antimicrobials 1 patient), respiratory disorders
244 (hospital acquired pneumonia, hospital acquired influenzae, respiratory deterioration, 3 patients) and
245 other events 2 patients.

246 **Mortality during the study**

247 Five patients included in the study died during their hospital stay, four from the PCT group and one
248 from the respiratory control group (age range 75-94 years). All had multiple co-morbidities including
249 cardiac (congestive cardiac failure, atrial fibrillation), renal and new or existing cancer diagnosis.
250 Antimicrobial treatment decisions for these patients were based on clinical decisions.

251 **Discussion**

252 This feasibility study of the introduction of PCT testing has shown a positive effect on antimicrobial
253 prescribing resulting in a decrease in the duration of antimicrobial courses in patients with RTIs and a
254 decrease in LOS without an increase in adverse events or re-admission to hospital. The median
255 duration of antimicrobial treatment was reduced from 8 to 7 days and antimicrobial consumption fell
256 by 9% when measured as DDD and DOT. This study confirms the findings of previous PCT trials^{28,44} that
257 it is an effective and worthwhile intervention to safely reduce antimicrobial exposure in patients with
258 RTIs and supporting the AMS programme. However, there were several findings which may have
259 influenced the outcomes and these need to be considered when viewing the overall results and
260 considering progression to and design of a full randomised controlled trial (RCT).

261 Overall PCT algorithm compliance was 35%, and compliance with stopping recommendations was 10%
262 when PCT levels were low (<0.25 µg/L). The reasons for non-compliance were clinical judgement (49%)
263 and meeting pre-determined over-riding criteria (51%). PCT was a new diagnostic test in the hospital
264 and physicians can require time to become familiar with and develop confidence in the use of PCT
265 testing.⁴⁵ Other studies have found algorithm compliance can be variable ranging from 35% to 80%.⁴⁴
266 An international, multicentre study found that centres with experience of using PCT and ongoing
267 reinforcement of PCT guided AMS had higher algorithm compliance than PCT naive centres.⁴⁴ Protocol
268 driven studies^{28,46} have also shown higher algorithm compliance and greater impact on antimicrobial
269 prescriptions than studies taking a quality improvement implementation approach.²⁹

270 Algorithm compliance must improve significantly in a future trial to maximise the potential impact of
271 PCT testing on antimicrobial prescribing decisions but also acknowledging the limitations of PCT and
272 that physicians cannot rely on PCT alone to guide antibiotic therapy.²³ In a future trial this should be
273 addressed by a more comprehensive educational programme and more effective incorporation into
274 the AMS programme to re-enforce PCT recommendations. Such an approach has been shown to be
275 effective^{30,46,47} and required for interventions such as PCT to realise their full benefit.¹⁹ The educational

276 element of this study may not have been sufficient. A future trial should consider the inclusion of more
277 frequent educational presentations prior to and during the intervention and include case reviews of
278 PCT patients. Consideration should be given to the development of pocket cards, incorporation into
279 local electronic antimicrobial prescribing guidelines and availability of results on the hospital
280 electronic laboratory system.⁴⁶

281 Delays in availability of PCT results may have also decreased the impact of the intervention and
282 contributed to poor algorithm compliance with 38% of PCT serum results not available until the next
283 day (24 hours after the serum sample was taken). This included results which were delayed or
284 unavailable for 12 patients until after they were discharged. In a future trial prompt availability of PCT
285 levels is important. This would allow physicians to consider PCT along with routine biochemistry and
286 blood analysis, and the patients' clinical parameters at the point of care when making antimicrobial
287 prescribing decisions. Consideration should be given to measurement of algorithm adherence at 48
288 hours to account for unforeseen delays PCT result availability or delayed physician review of PCT
289 results.

290 There were several factors involved in patient recruitment which may have influenced the primary
291 outcomes of the study and should be addressed in a future trial design. These were the variation in
292 infection severity between the PCT and respiratory control groups and the inclusion of patients who
293 were already prescribed antimicrobials prior to hospital admission. These factors can be addressed in
294 a suitably powered future RCT with the inclusion of illness severity scores, along with the use of
295 multivariate and sub-group analysis.

296 A future RCT would include a broader range of physicians rather than respiratory specialists alone.
297 Antimicrobial consumption in the general control group of patients in this study was higher than in
298 either of the respiratory groups. The addition of a PCT testing to the existing AMS programme may
299 have the potential to have a greater impact on this patient group.

300

301 **Strengths and limitations**

302 The study was conducted in a setting where PCT was a newly available test to physicians. A broad
303 range of RTIs were recruited and the study took place over a calendar year and included seasonal
304 variation in illness and prescribing. Patients were randomised to intervention or control, thus reducing
305 selection bias. Serial PCT measurements were available to guide antimicrobial prescribing.

306 The study had some limitations. The study population had a clinical need for antimicrobial treatment
307 so the study was designed to examine the duration of therapy and LOS, rather than investigating the
308 potential to withhold antimicrobial therapy. The study results may have been influenced by a study
309 effect. Both the PCT and respiratory control groups were treated by the same group of physicians who
310 all received education and as they were aware that their behaviour was being monitored which may
311 have resulted in a Hawthorn effect.⁴⁸ The intervention was limited to one medical speciality which
312 may limit its generalisability to other medical specialties and settings. The need for consent and PCT
313 results which were not available at the point of clinical decision making in a small number of cases.

314

315 **Conclusion**

316 PCT testing had a positive effect on antimicrobial prescribing during this feasibility study. Several
317 factors were identified which may have influenced the outcomes and the intervention
318 implementation. The successful implementation of PCT testing requires an ongoing comprehensive
319 education programme, greater integration into the AMS programme and delivery of PCT results in a
320 timely manner. This feasibility study has shown that a larger randomised controlled trial would be
321 beneficial to further explore the positive aspects of these findings.

322

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328

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332

333 **Transparency declarations**

334 Nothing to declare.

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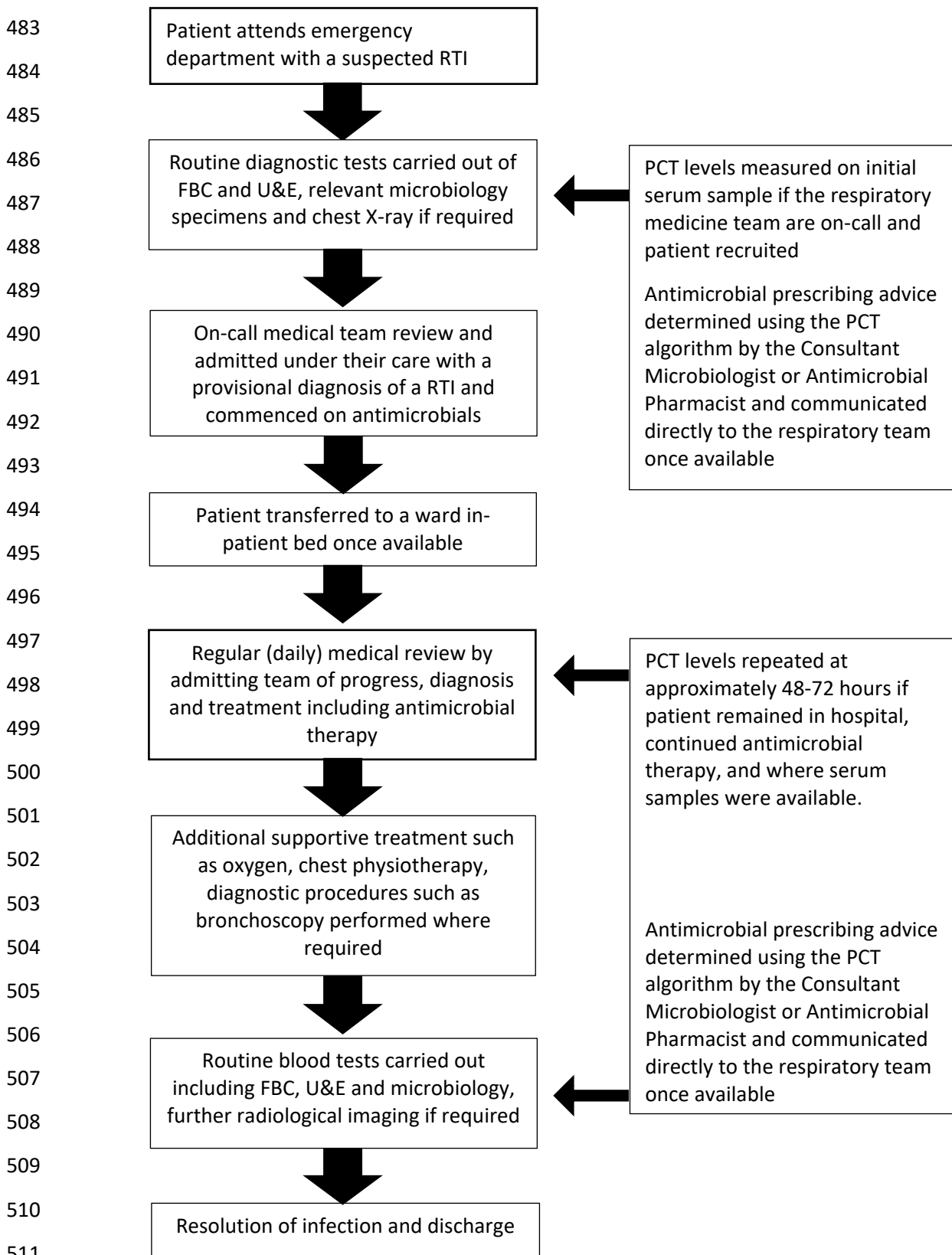
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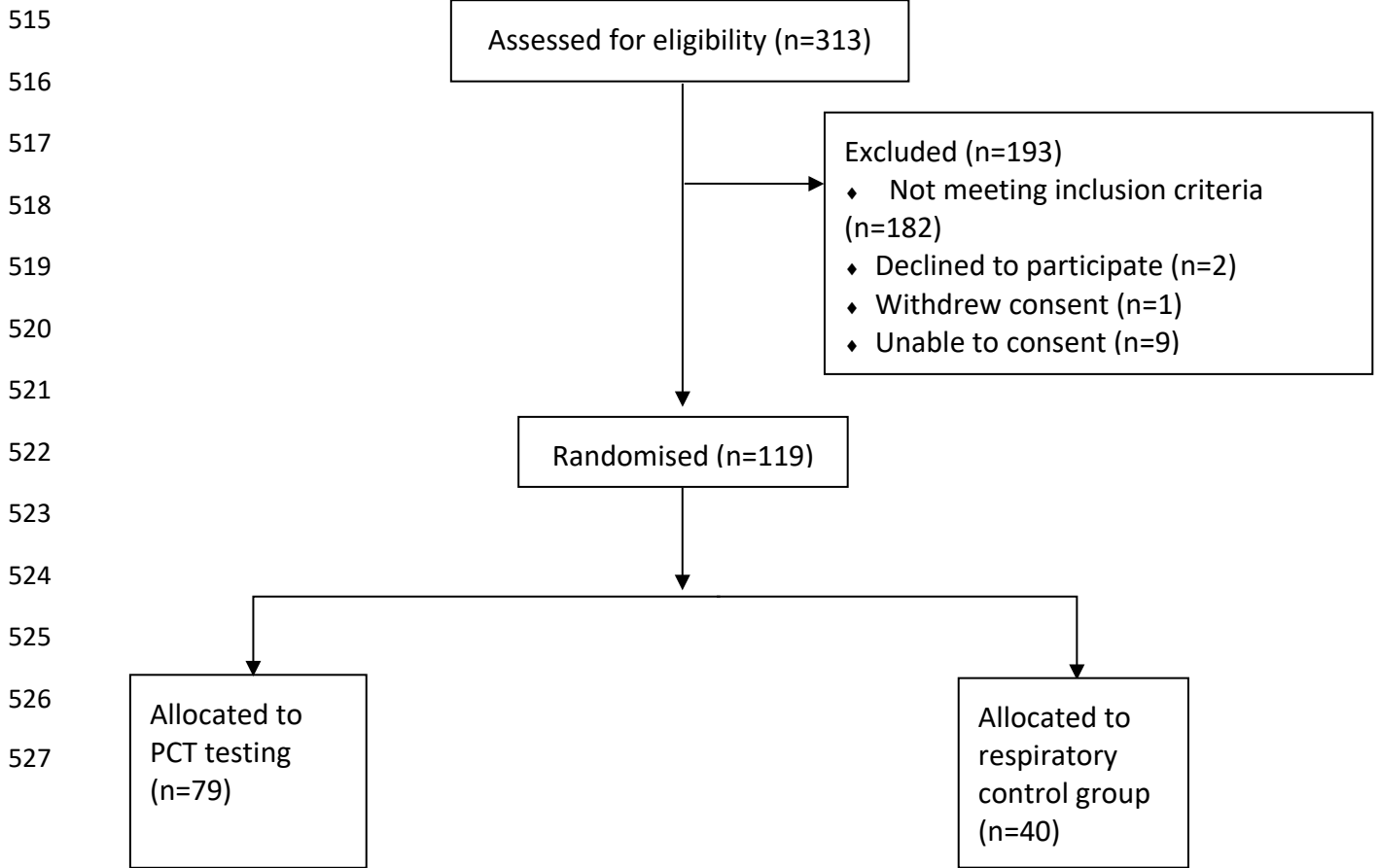
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482 **Figure 1 Patient hospital journey with a respiratory tract infection**



512 RTI: Respiratory tract infection, PCT: procalcitonin, FBC: full blood count, U&E: urea and
513 electrolytes

514 **Figure 2. CONSORT 2010 Flow Diagram**



528 **Table 1. Demographic data and study overview**

Variable		Study Group			
		Overall	PCT arm	Respiratory Control arm	General Control arm
Participants		167 (100%)	79 (47.3%)	40 (24.0%)	48 (28.7%)
Gender	Female	79 (47.3%)	31 (39.2%)	23 (57.5%)	25 (52.1%)
	Male	88 (52.7%)	48 (60.8%)	17 (42.5%)	23 (47.9%)
Age (years)		68.7 ± 14	68.6 ± 13.6	68.4 ± 15.3	69.1 ± 13.9
Co-existing conditions and risk factors					
Smoking Status	Non-smoker	50 (30.3%)	26 (32.9%)	13 (32.5%)	11 (23.9%)
	Smoker	33 (20%)	20 (25.3%)	5 (12.5%)	8 (17.4%)
	Ex-smoker	82 (49.7%)	33 (41.8%)	22 (55%)	27 (58.7%)
Asthma		28 (16.8%)	13 (16.5%)	10 (25%)	5 (10.4%)
COPD A-C		58 (34.7%)	23 (29.1%)	10 (25%)	25 (52%)
COPD D		24 (14.4%)	10 (12.7%)	5 (12.5%)	9 (18.8%)
Bronchiectasis		16 (9.6%)	9 (11.4%)	3 (7.5%)	4 (8.3%)
Interstitial lung disease		7 (4.2%)	4 (5%)	2 (5%)	1 (2.1%)
Final diagnosis					
Asthma		11 (6.6%)	3 (3.8%)	6 (15%)	2 (4.2%)
Community acquired pneumonia		18 (10.8%)	8 (10%)	3 (7.5%)	7 (14.6%)
COPD		62 (37.1%)	24 (30.4%)	13 (32.5%)	25 (52%)
Lower respiratory tract infection		45 (27%)	28 (35.4%)	7 (17.5%)	10 (20.8%)
Other lower respiratory tract infections		20 (12%)	10 (12.6%)	7 (17.5%)	3 (6.2%)
Non-respiratory related		11 (6.6%)	6 (7.6%)	4 (10%)	1 (2.1%)

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530

531 **Table 2. Clinical findings on admission to hospital***

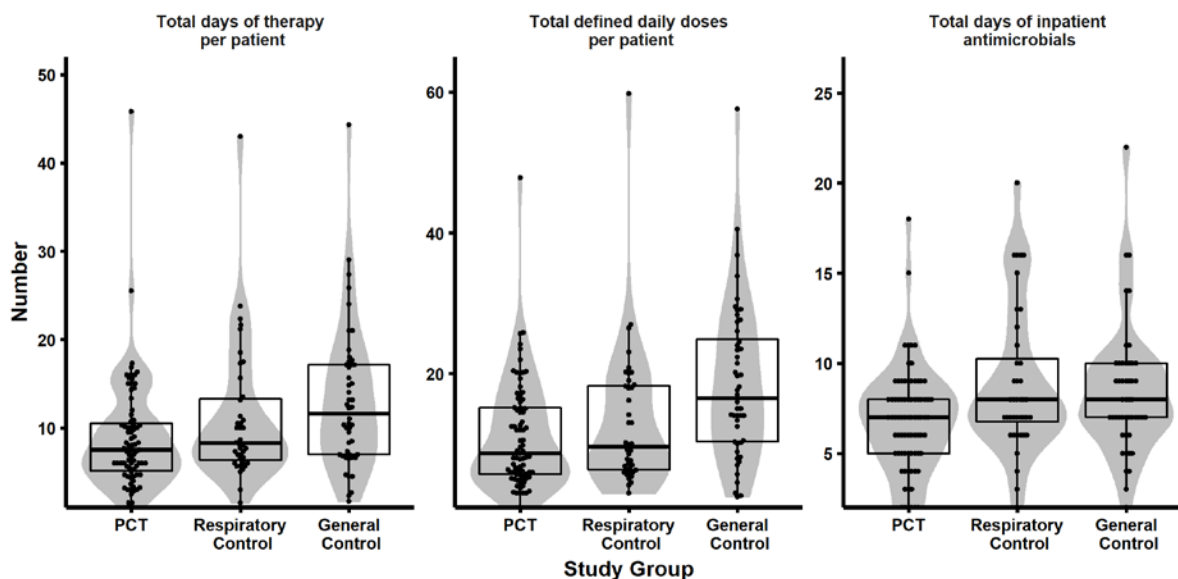
	Total (n = 167)	PCT (n = 79)	Respiratory Control (n = 40)	General control (n = 48)
Respiratory rate- breaths/minute	22.1 ± 5	22.1 ± 5.4	21.1 ± 3.7	22.7 ± 5.2
Systolic blood pressure- mmHg	133 ± 23.1	130.9 ± 22.9	136 ± 20.9	134 ± 25
Diastolic blood pressure- mmHg	75 ± 14.1	74.8 ± 12	78.6 ± 14.8	72.3 ± 16.1
Heart rate- beats/minute	91.8 ± 20.1	93.4 ± 23.3	91.2 ± 16.7	89.8 ± 16.7
Temperature- °C	36.8 ± 0.8	36.8 ± 0.8	36.9 ± 0.8	36.8 ± 0.9
Rigors - no. (%)	24 (14.4%)	11 (13.9%)	6 (15%)	7 (14.6%)
Fever - no. (%)	18 (10.8%)	8 (10.1%)	5 (12.5%)	5 (10.4%)
Chills - no. (%)	15 (9%)	10 (12.7%)	1 (2.5%)	4 (8.3%)
Number of clinical signs of infection	1.8 ± 1.3	1.9 ± 1.3	1.7 ± 1.2	1.8 ± 1.3
Documented signs of respiratory illness				
Cough - no. (%)	132 (79%)	64 (81%)	31 (77.5%)	37 (77%)
Shortness of breath - no. (%)	101 (60.5%)	45 (57%)	23 (57.5%)	33 (68.7%)
Productive of sputum - no. (%)	81 (48.5%)	39 (49.4%)	15 (37.5%)	27 (56.2%)
Dyspnoea - no. (%)	49 (29.3%)	22 (27.8%)	10 (25%)	17 (35.4%)
Pleuritic pain - no. (%)	26 (15.6%)	10 (12.7%)	9 (22.5%)	7 (14.6%)
Respiratory failure - no. (%)	19 (11.4%)	8 (10.1%)	5 (12.5%)	6 (12.5%)
Abnormal chest exam - no. (%)	144 (86.2%)	70 (88.6%)	31 (77.5%)	43 (89.6%)
Abnormal radiological findings - no. (%)	94 (56.3%)	42 (53.2%)	21 (52.5%)	28 (58.3%)
CURB-65 score (CAP patients)	1.56 ± 1.05	1.87 ± 1.05	0.66 ± 0.47	1.57 ± 1.05
Number of signs of acute respiratory illness	3.9 ± 1.4	3.8 ± 1.4	3.8 ± 1.4	4 ± 1.3
Antimicrobials prescribed pre-admission - no. (%)				
Antimicrobials prescribed pre-admission - no. (%)	59 (35.3%)	28 (35.4%)	10 (25%)	21 (43.7%)
Corticosteroids prescribed pre-admission - no. (%)				
Corticosteroids prescribed pre-admission - no. (%)	34 (20.4%)	14 (17.7%)	7 (17.5%)	13 (27%)
Infection source				
Community - no. (%)	149 (89.2%)	70 (88.6%)	32 (80%)	47 (98%)
Healthcare - no. (%)	13 (7.8%)	6 (7.6%)	6 (15%)	1 (2%)
Hospital - no. (%)	5 (3%)	3 (3.8%)	2 (5%)	0 (0%)

532 *plus minus values are means + SD

533 **Table 3. Primary and secondary outcome data**

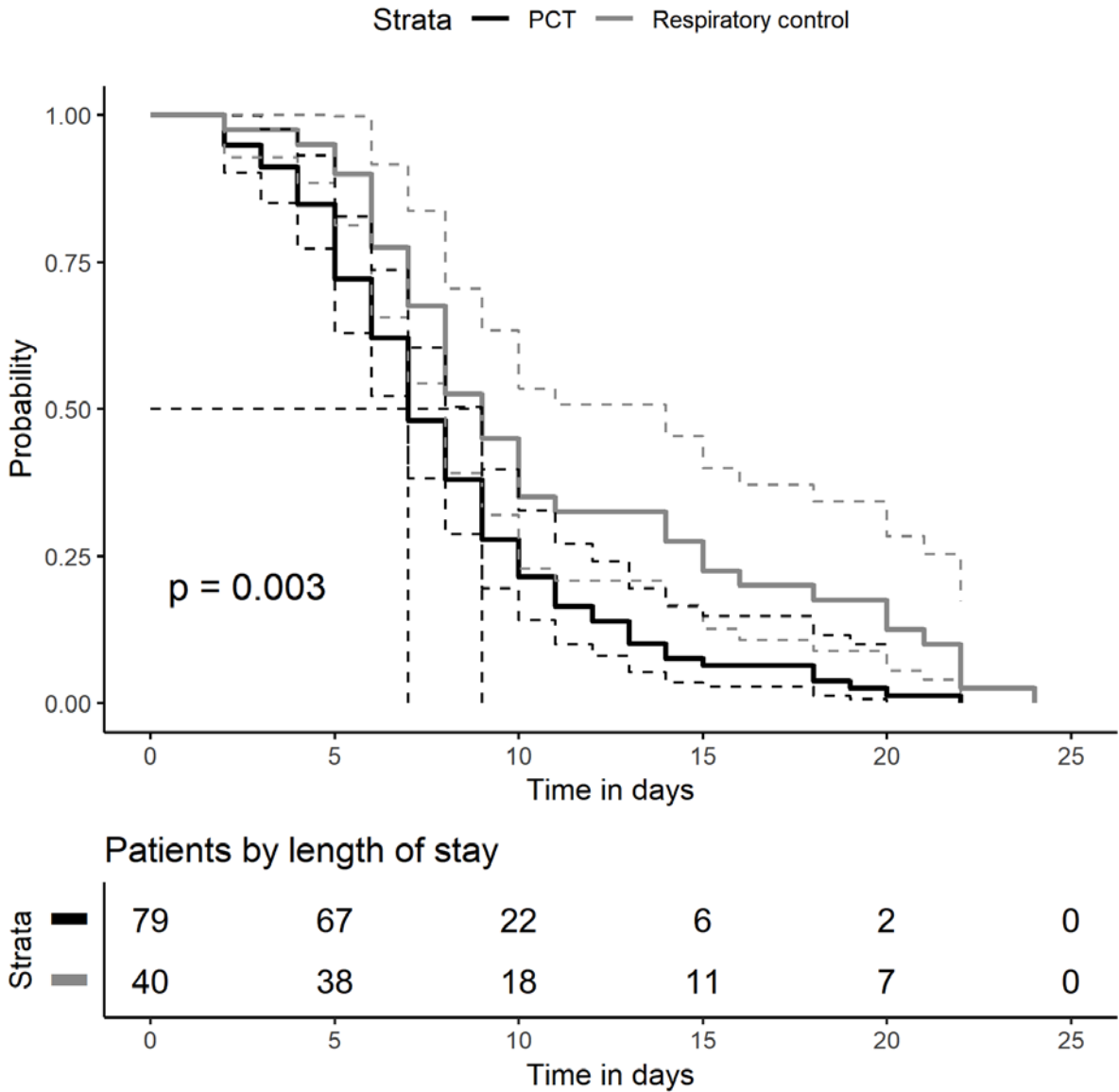
Primary outcomes Mean ± SD (Median)	PCT (n = 79)	Respiratory Control (n = 40)	General control (n = 48)	p value
Defined daily doses per patient	11.1 ± 7.5 (8.66)	13.1 ± 10.7 (9.57)	18.5 ± 11 (16.5)	0.218
Days of therapy per patient	8.9 ± 6.3 (7.5)	11 ± 7.6 (8.25)	13.7 ± 11.1 (11.63)	0.077
Total duration of inpatient antimicrobials (days)	6.8 ± 2.8 (7)	8.9 ± 4 (8)	8.4 ± 3.6 (8)	0.0125*
Length of hospital stay (days)	7.4 ± 4.3 (7)	10.5 ± 6.1 (8)	8.9 ± 3.8 (8)	0.009*
Secondary outcomes				
Hospital readmission within 30 days	7 (8.9%)	8 (20%)	7 (14.6%)	0.1507
Relapse of infection within 30 days	6 (7.6%)	8 (20%)	6 (12.5%)	0.0924
Adverse events	6 (7.6%)	3 (7.5%)	4 (8.3%)	0.9852

534 *= statistical significance was set as <0.05, p-values relate to the comparison between the PCT and
 535 respiratory control groups



536
 537
 538 **Figure 3. Main antimicrobial consumption outcomes.**

539



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542 **Figure 4. Comparison of time to discharge probability for PCT versus respiratory control arms-**

543 **Kaplan–Meier curves. Median probability of discharge is given by the horizontal dashed line.**

544

545 **Table 4. PCT algorithm compliance**

PCT level (µg/L)	Algorithm recommendation	Number of patients	Number of PCT test results	Number of patients compliant with algorithm	Number of patients non-compliant with algorithm	Percentage of patients compliant with algorithm
≤0.05 to <0.25	Antimicrobial therapy discouraged	67	119	7	60	10%
≥0.25	Antimicrobial therapy encouraged	25	44	25	0	100%

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