

1 **Title page**

2 **Full title**

3 Impact of antibiotic treatment duration on outcomes in older men with suspected  
4 urinary tract infection: retrospective cohort study

5 **Running title**

6 Antibiotic duration for UTI in older men

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18 **Keywords**

19 Urinary tract infection; aged; electronic health records; primary care; men

20 **Key points**

- 21
- 22 • Clinical guidelines recommend at least seven days of antibiotic treatment for  
23 urinary tract infection in men, but this is largely based on expert opinion.
  - 24 • It is not known if shorter durations of antibiotic treatment are as safe or effective  
as seven days.

- 25       • We used linked health data from the UK to estimate the risk of treatment failure,  
26       hospitalisation and death in older men presenting to primary care with  
27       suspected urinary tract infection, who were prescribed different durations of  
28       antibiotic treatment.
- 29       • We found that 3-day antibiotic treatment was associated with an increased risk  
30       of treatment failure but a reduced risk of acute kidney injury.
- 31       • These findings support the need for a definitive randomised trial of short versus  
32       standard duration treatment.

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35   Findings from this research were presented at the General Practice Research in  
36   Infections Network meeting in Utrecht, The Netherlands, on 5<sup>th</sup> October 2018.

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48 **Abstract**

49 **Purpose**

50 Clinical guidelines recommend at least seven days of antibiotic treatment for older  
51 men with urinary tract infection (UTI). There may be potential benefits for patients,  
52 health services and antimicrobial stewardship if shorter antibiotic treatment resulted in  
53 similar outcomes. We aimed to determine if treatment duration could be reduced by  
54 estimating risk of adverse outcomes according to different prescription durations.

55 **Methods**

56 This retrospective cohort study included men aged  $\geq 65$  years with a suspected UTI.  
57 We compared outcomes in men prescribed 3, 5, 7 and 8-14 days of antibiotic treatment  
58 in a multivariable logistic regression analysis, and 3 versus 7 days in a propensity-  
59 score matched analysis. Our outcomes were re-consultation and re-prescription  
60 (proxy for treatment failure), hospitalisation for UTI, sepsis, or acute kidney injury  
61 (AKI), and death.

62 **Results**

63 Of 360,640 men aged  $\geq 65$  years, 33,745 (9.4%) had a UTI. Compared to 7-days, men  
64 prescribed 3-day treatment had greater odds of re-consultation and re-prescription  
65 (adjusted OR 1.48, 95% CI 1.25-1.74) but lower odds of AKI hospitalisation (adjusted  
66 OR 0.66, 95% CI 0.45-0.97). We estimated that treating 150 older men with 3-days  
67 instead of 7-days of antibiotics could result in four extra re-consultation and re-  
68 prescriptions and one less AKI hospitalisation. We estimated annual prescription cost  
69 savings at around £2.2 million.

70 **Conclusions**

71 Antibiotic treatment for older men with suspected UTI could be reduced to 3-days,  
72 albeit with a small increase in risk of treatment failure. A definitive randomised trial is  
73 urgently needed.

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95 **Main text**

96 **Introduction**

97 Urinary tract infections (UTIs) represent an important cause of morbidity and antibiotic  
98 use in older men. Around 20% of all UTIs occur in men.<sup>1</sup> Incidence increases with age  
99 from around 3 episodes per 100 person-years in men aged 65-74, to 8-11 episodes  
100 per 100 person-years in men aged  $\geq 85$ .<sup>2, 3</sup>

101 The optimal duration of antibiotic treatment for UTI in older men is not known.<sup>4</sup> Most  
102 clinical guidelines recommend seven days of antibiotic treatment.<sup>5-7</sup> This  
103 recommendation is largely based on expert consensus due to the lack of data in this  
104 area. Previous randomised trials investigating different antibiotic durations for UTI in  
105 men have focussed on febrile <sup>8, 9</sup> or complicated UTI,<sup>10, 11</sup> or men with spinal cord  
106 injury,<sup>12</sup> and are not generalizable to the majority of men with community-acquired UTI  
107 seen and treated in primary or ambulatory care settings.

108 Antimicrobial stewardship policies and guidelines recommend prescribing the  
109 minimum duration of antibiotic treatment required for clinical resolution.<sup>13, 14</sup> Two  
110 recent studies indicate that antibiotic treatment duration for UTI in older men could be  
111 reduced. First, a retrospective study of UK health records found that around 20% of  
112 older men presenting to primary care with a UTI were prescribed  $< 7$  days of antibiotics,  
113 suggesting that some clinicians may already be prescribing shorter treatment to  
114 selected men.<sup>2</sup> Second, an observational study found no difference in the rate of  
115 clinical recurrence between US male Veterans with UTI prescribed long course ( $> 7$   
116 days) versus short course treatment ( $\leq 7$  days).<sup>15</sup> However, this study used outpatient  
117 data only and therefore may have missed men who were subsequently hospitalised  
118 with UTI-related emergencies, such as sepsis or acute kidney injury.

119 We therefore used anonymised linked health records that spanned primary care,  
120 secondary care and death registry data, to estimate risk of adverse outcomes in older  
121 men prescribed different durations of antibiotic treatment for UTI in primary care. Our  
122 aim was to assess whether short course treatment was associated with an increased  
123 risk of adverse events to determine the potential for safe and effective reduction of  
124 antibiotic treatment duration.

## 125 **Patients and Methods**

### 126 **Data Source**

127 We used the Clinical Practice Research Datalink (CPRD), an electronic database of  
128 anonymised primary care records, covering 11.3 million patients from 674 general  
129 practices across the UK.<sup>16</sup> Approximately 7% of the UK population are included and  
130 patients are broadly representative of the wider UK population in terms of age, gender  
131 and ethnicity. The CPRD holds data on demographics, clinical encounters and  
132 diagnoses (coded using Read codes), drug prescriptions, laboratory tests and referrals  
133 to specialists. Data are available once the primary care records have met a series of  
134 quality checks on completeness and reliability and the CPRD deems them to be of a  
135 required standard for research purposes. Linked hospital and death registration data  
136 are available for patients from approximately 50% of contributing English practices.  
137 Hospital diagnoses and causes of death are recorded using version 10 of the  
138 International Classification of Disease (ICD-10).

139 The CPRD Independent Scientific Advisory Committee approved the study protocol  
140 (protocol number 17\_250). Further ethical approval was not required as the proposed  
141 research was within the remit of the CPRD's broad National Research Ethics Service  
142 approval. We used the Reporting of Studies Conducted using Observational

143 Routinely-collected Health Data (RECORD) statement and checklist to guide study  
144 reporting.<sup>17</sup>

### 145 **Design and participants**

146 This was a retrospective cohort study using linked health record data. Men were  
147 eligible for inclusion if, between 1<sup>st</sup> January 2010 and 31<sup>st</sup> December 2016, their data  
148 were of the quality required by CPRD, they were  $\geq 65$  years old, were registered with  
149 a practice that had consented to linkage to hospital and death registry data, and had  
150 a primary care record of an incident UTI. Follow-up began from the latest of, study  
151 start date (1<sup>st</sup> January 2010), patient's 65<sup>th</sup> birthday, six months after they registered  
152 with the practice (to avoid including historical UTIs recorded at registration), or the  
153 date their practice met the CPRD data quality requirements. Follow-up ended on the  
154 earliest of study end date (31<sup>st</sup> December 2016), the day the patient died or transferred  
155 out of the practice (i.e. last date of CPRD data collection), or 28 days after an incident  
156 UTI event. We excluded men who were temporary residents, or had gaps in their data  
157 coverage. We defined 'incident' as an event occurring in a man without a UTI-related  
158 Read code or trimethoprim or nitrofurantoin prescription in the preceding 90 days. We  
159 defined UTI as the presence of a symptom code (e.g., "dysuria") or diagnostic code  
160 (e.g., "cystitis") relevant to UTI (codes available in Supplementary Appendix 1), and a  
161 same-day prescription code indicating prescribing of a relevant antibiotic. We  
162 restricted the analyses to the first incident UTI identified during a patient's follow-up  
163 period.

### 164 **Exposure**

165 We used prescription data for daily dosing and total quantity prescribed to calculate  
166 duration of antibiotic prescriptions as a proxy for duration of treatment. We excluded

167 prescriptions with durations >14 days as it is unlikely that these were prescribed for  
168 an acute UTI, and more likely that they reflected treatment for prostatitis. We also  
169 excluded prescription durations of 1, 2, 4, and 6 days, as together these represented  
170 <1% of all calculated durations and were potentially unreliable. The final exposure  
171 groups were 3, 5, 7 and 8-14 days.

## 172 **Outcomes**

173 We assessed the impact of antibiotic prescription duration on:

- 174 1. Re-consultation for urinary symptoms and a same-day antibiotic prescription  
175 within 14 days following the incident UTI, as a proxy for treatment non-  
176 response, ascertained through Read and prescription codes recorded in  
177 primary care records.
- 178 2. Hospitalisation for UTI, sepsis, or acute kidney injury (AKI) within 14 days  
179 following the incident UTI ascertained from ICD-10 codes recorded in linked  
180 hospital admission data for the first episode of a hospital admission, i.e., the  
181 episode most likely responsible for the admission.
- 182 3. Death within 28 days following the incident UTI using linked death registration  
183 data.

## 184 **Statistical Analyses**

185 We used primary care demographic and clinical codes to describe baseline  
186 characteristics for patients by prescription duration. Firstly, we assessed the impact of  
187 different prescription durations by calculating odds ratios (OR) and 95% confidence  
188 intervals (CI) for the risk of each outcome in those prescribed 7-day treatment,  
189 compared to those prescribed 3, 5 or 8-14 days treatment. We adjusted for potential  
190 confounders of the association between antibiotic duration and outcome, including the

191 choice of antibiotic, age, Index of Multiple Deprivation score quintile, Charlson  
192 comorbidity score, polypharmacy (defined as records indicating  $\geq 5$  long-term  
193 medications per month in the year prior to the incident UTI), and the presence or  
194 absence of a record indicating diabetes, dementia, coronary heart disease, stroke,  
195 cancer, heart failure, renal disease, benign prostatic hyperplasia, and prostate cancer.

196 Secondly, we compared outcomes in men prescribed 3-day versus 7-day treatment  
197 using propensity score matching to improve balance of baseline covariates across the  
198 two treatment groups. We chose 7 days as the reference standard as it is currently the  
199 recommended treatment duration for male UTI in the UK, and 3 days as the  
200 comparator as it is a potentially acceptable and feasible shorter duration of treatment,  
201 given that 3-day treatment is widely used to treat UTI in women. Men were matched  
202 on a range of demographic and clinical variables related to their propensity to receive  
203 a 7-day prescription. We used nearest neighbour matching with no replacement and  
204 matched each patient with a 3-day prescription to three patients with a 7-day  
205 prescription. We assessed balance in measured baseline covariates between  
206 matched groups by visually inspecting jitter plots and histograms of covariate  
207 distribution before and after matching, and by calculating standardised mean  
208 differences for covariates between groups. We regarded standardised mean  
209 differences of  $< 0.1$  as reflecting adequate balance.<sup>18, 19</sup>

210 We used mixed effects models in both analyses to account for clustering by general  
211 practice. We repeated the analyses restricting to men prescribed trimethoprim, the  
212 most commonly used antibiotic for UTI in the UK during the study period. Finally, we  
213 calculated E-values to estimate the minimum effect size required by an unmeasured  
214 confounder to fully explain away any statistically significant associations.<sup>20</sup> All  
215 statistical tests were 2-sided with  $p < 0.05$  considered statistically significant but an

216 effect size of 10% considered clinically significant. Analyses were conducted in R  
217 version 3.2.1.

## 218 **Results**

219 From a cohort of 360,640 men aged 65 and over with a median follow-up of 4.9 years  
220 (Interquartile range (IQR), 3.1-6.4), we identified 33,745 (9.4%) with an incident UTI  
221 treated with a relevant antibiotic (Figure 1). Of these, we were able to assign an  
222 antibiotic prescription duration to 32,593 (96.6%) incident UTIs. The median age at the  
223 time of incident UTI was 77 years (IQR, 70 - 83). In total, 1966 (6.0%) men were  
224 prescribed amoxicillin, 2002 (6.1%) ciprofloxacin, 2060 (6.3%) cefalexin, 2143 (6.6%)  
225 co-amoxiclav, 5724 (17.6%) nitrofurantoin, and 18,698 (57.4%) trimethoprim.  
226 Guideline concordant 7-day treatment was prescribed to 20,729 (63.6%) men, 3-day  
227 treatment to 2498 (7.7%), 5-day treatment to 6254 (19.2%), and 8-14 days to 3112  
228 (9.5%). Practices varied in their prescribing of the different antibiotic durations. Of all  
229 antibiotic prescriptions for UTI in older men, the median proportion prescribed 3-day  
230 treatment was 5.1% (IQR, 1.8-10.8), 5-day treatment was 14.6% (IQR, 7.7-25.4), 7-  
231 day treatment was 65.4% (IQR, 53.1-76.2), and >7day treatment was 8.3% (IQR, 3.8-  
232 14.8). Baseline comorbidities were broadly similar across the different treatment  
233 duration groups (Table 1).

## 234 **Outcomes according to treatment duration**

235 A total of 2007 (6.2%) men re-consulted and received another antibiotic prescription  
236 within 14 days following the incident UTI. Compared to 7-day prescriptions, there was  
237 a graded association between prescription duration and odds of re-consultation and  
238 re-prescription with adjusted ORs of 1.48 (95% CI 1.25-1.74) for 3-day prescriptions,  
239 1.18 (95% CI 1.04-1.33) for 5-day prescriptions, and 0.80 (95% CI 0.67-0.96) for 8-14

240 day prescriptions (Table 2). The re-prescribed antibiotics were made up of a lower  
241 proportion of trimethoprim, similar proportion of amoxicillin, and greater proportions of  
242 the other antibiotics (Supplementary Table 1).

243 A total of 817 (2.5%) men were hospitalised for UTI, 89 (0.3%) hospitalised for sepsis,  
244 and 449 (1.4%) hospitalised for AKI within 14 days following the incident UTI. There  
245 were no significant associations between antibiotic prescription duration and  
246 hospitalisation for UTI or sepsis. Compared to 7-days, 3 and 8-14 day prescriptions  
247 were associated with reduced odds of hospitalisation for AKI (adjusted OR for 3-days,  
248 0.66, 95% CI 0.45-0.97, adjusted OR for 8-14 days, 0.63, 95% CI 0.40-0.99). A total  
249 of 419 (1.3%) men died within 28 days of the incident UTI. There were no significant  
250 associations between antibiotic prescription duration and odds of death.

### 251 **Propensity score matched comparison of 7-day versus 3-day therapy**

252 We matched 2392 men prescribed 3-day treatment to 7182 men prescribed 7-day  
253 treatment. Inspection of jitter plots and histograms suggested matching had improved  
254 balance of covariates across the two groups. Standardised mean differences were all  
255 less than 0.1 (Table 3). 3-day prescriptions were associated with increased odds of  
256 re-consultation and re-prescription (OR 1.52, 95% CI 1.25-1.85) and reduced odds of  
257 hospitalisation for AKI (OR 0.62, 95% CI 0.42-0.93) (Table 4).

258 Using the propensity score matched event rates and ORs in table 4, we estimate that  
259 treating 150 older men with 3-day instead of 7-day treatment, could result in four extra  
260 re-consultation and re-prescriptions (numbers needed to harm = 37) and one less AKI  
261 hospital admission (numbers needed to treat = 148).<sup>22</sup> Our previous study showed  
262 that around 7% of a sample of roughly 400,000 men  $\geq 65$  were prescribed an antibiotic  
263 in primary care for UTI in 2014.<sup>2</sup> Current UK population estimates suggest there are

264 around 5.2 million men aged  $\geq 65$ .<sup>23</sup> A 7% annual UTI rate equates to around 364,000  
265 UTI events. Based on current prescribing costs reported in the British National  
266 Formulary (3-day trimethoprim = £3.60, 7-day trimethoprim = £10.00, 7-day  
267 nitrofurantoin = £9.50), if all men were prescribed 3-days of trimethoprim instead of 7  
268 days, and men who re-consulted were prescribed 7 days of nitrofurantoin, the UK  
269 health service could save around £2.2 million a year.

## 270 **Sensitivity analyses**

271 We repeated the analyses restricting to men who received trimethoprim and found that  
272 all ORs were consistent with our main analyses. We calculated E-values for the two  
273 significant associations in our propensity-score matched analysis. The E-value was  
274 2.4 for re-consultation and re-prescription, and 2.6 for AKI hospitalisation, suggesting  
275 any unmeasured confounder would require an OR of at least 2.4 for its association  
276 with antibiotic prescription duration and outcome, independent of measured  
277 confounders, to explain away the observed associations.

## 278 **Discussion**

279 We showed, for the first time, that in older men presenting to primary care with a UTI,  
280 3-day antibiotic treatment was associated with a 52% increase in odds of re-  
281 consultation and re-prescription that may indicate treatment failure or recurrent  
282 infection, but was not associated with increased odds of UTI-related hospitalisation or  
283 death. We also showed for the first time, an association between 3-day treatment and  
284 a 38% reduction in the odds of hospitalisation for AKI.

## 285 **Results in context**

286 A retrospective observational study of 33,336 index UTIs in US male Veterans found  
287 no difference in recurrence rates at 30 days between short and long duration antibiotic

288 treatment.<sup>15</sup> Similar to our study, patients did not require microbiological confirmation  
289 of UTI and were included if they had a relevant diagnostic code and antibiotic  
290 prescription. However, this study defined 'short duration' as  $\leq 7$  days, and 77% of the  
291 short duration group received 7-day treatment. Thus, their comparison was  $\leq 7$  days  
292 versus  $>7$  days, and explains the discrepancy between our finding of increased odds  
293 of re-consulting and receiving another antibiotic prescription in short duration (3 or 5-  
294 day) versus long duration (7-day) treatment.

295 Our finding of an association between 3-day antibiotic treatment and reduced odds of  
296 AKI could be explained by trimethoprim prescribing. Trimethoprim is associated with  
297 hyperkalaemia and AKI in older adults.<sup>21</sup> In our unmatched multivariable logistic  
298 regression analysis, the risk of AKI was reduced in the group with the shortest  
299 exposure to trimethoprim (3-day treatment) and the group with the lowest proportion  
300 of trimethoprim use (8-14 day group, 16.8% prescribed trimethoprim versus 60% in  
301 the 7-day group). In our propensity-score matched analysis, 85% of men in the 3 and  
302 the 7-day treatment groups were prescribed trimethoprim, but there was again a  
303 reduced risk of AKI in the 3-day group, supporting an association between shorter  
304 trimethoprim exposure and reduced risk of AKI.

305 Few randomised trials have investigated the potential for shorter duration of antibiotic  
306 treatment in men with UTI, and those that have focussed on more severe UTI. A  
307 Swedish trial of 114 men with febrile UTI showed similar clinical and microbiological  
308 cure rates between 14-day and 28-day antibiotic treatment.<sup>9</sup> A randomised placebo  
309 controlled non-inferiority trial recruited men with febrile UTI from Dutch primary care  
310 and emergency departments, and showed 7-day antibiotic treatment was inferior to  
311 14-day treatment in terms of clinical cure rates 10-18 days post UTI.<sup>8</sup> In contrast, a US  
312 trial of men and women (39% men) with complicated UTI or acute pyelonephritis

313 showed no difference in outcomes between those receiving 5-day versus 10-day  
314 antibiotic treatment.<sup>10</sup> However, these trials recruited men with more severe UTI than  
315 that normally seen in a primary care setting. To the best of our knowledge, no trials  
316 have investigated the effect of short duration antibiotic treatment for men presenting  
317 to primary care with symptoms suggestive of UTI, but without fever or other signs of  
318 ascending infection.

### 319 **Strengths and weaknesses of this study**

320 We used data from a general practice database that is broadly representative of the  
321 UK population.<sup>16</sup> Cohort entry was dependent on presentation and empirical treatment  
322 of UTI in primary care, and thus reduced indication bias. We also reduced indication  
323 bias by matching patients on their propensity to receive a 7-day prescription, and  
324 achieving adequate balance of covariates across treatment groups.

325 Our study has important limitations. We attempted to capture patients presenting with  
326 UTI but had no microbiological data to support this. However, whilst a limitation, this  
327 is also more representative of clinical practice. Our estimates are based on  
328 *prescription* duration and may overestimate actual antibiotic consumption. Despite  
329 careful selection of codes used to identify eligible men, differential use of codes  
330 amongst clinicians means we may have included some men who had more  
331 complicated UTI or pyelonephritis. Our finding of an increase in the rate of UTI-related  
332 re-consultation and re-prescription among men prescribed 3-day treatment may be  
333 due to planned follow-up for those prescribed shorter courses. Furthermore, whilst  
334 some of these events may represent 'treatment failure', others may reflect different  
335 expectations about the speed of symptom resolution. Finally, despite our design,  
336 differential coding, indication bias and residual confounding may still have affected our

337 findings. However, our E-values suggest residual confounders would need relatively  
338 strong associations between antibiotic duration and outcomes to alter the conclusions  
339 from our effect estimates.

## 340 **Conclusions**

341 Our findings suggest it may be possible to safely reduce the duration of antibiotic  
342 treatment to 3 days for older men presenting to primary care with a UTI. For patients,  
343 shorter duration treatment could mean better adherence and less side effects. Other  
344 potential benefits may include a reduction in AKI-related hospitalisations, antibiotic  
345 burden, and prescription costs. Potential harms include a possible increased risk of  
346 treatment failure. A definitive randomised trial is needed to compare short versus  
347 standard treatment duration of a specific antibiotic for UTI in men.

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372 **Transparency declaration**

373 All authors have completed the ICMJE uniform disclosure form at  
374 [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for  
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468 **Tables**

469 Table 1. Baseline characteristics according to antibiotic prescription duration. Values  
470 are numbers (%) unless otherwise stated.

	<b>Antibiotic prescription duration</b>			
	<b>3 days</b>	<b>5 days</b>	<b>7 days</b>	<b>8-14 days</b>
<b>Number (%) of prescriptions</b>	2498 (7.7)	6254 (19.2)	20729 (63.6)	3112 (9.5)
<b>Mean (SD) age</b>	77.4 (8.0)	77.7 (8.1)	76.9 (7.9)	76.7 (7.8)
<b>Antibiotic choice</b>				
Amoxicillin	12 (0.5)	512 (8.2)	1392 (6.7)	50 (1.6)
Cefalexin	60 (2.4)	262 (4.2)	1133 (5.5)	605 (19.4)
Ciprofloxacin	38 (1.5)	852 (13.6)	649 (3.1)	463 (14.9)
Co-amoxiclav	13 (0.5)	195 (3.1)	1843 (8.9)	92 (3.0)
Nitrofurantoin	241 (9.6)	802 (12.8)	3301 (15.9)	1380 (44.3)
Trimethoprim	2134 (85.0)	3631 (58.1)	12411 (59.9)	522 (16.8)
<b>Index of multiple deprivation decile</b>				
1 or 2 (least deprived)	527 (21.1)	1670 (26.7)	5217 (25.2)	890 (28.6)
3 or 4	552 (22.1)	1494 (23.9)	5016 (24.2)	764 (24.6)
5 or 6	599 (24.0)	1398 (22.4)	4568 (22.0)	655 (21.0)
7 or 8	427 (17.1)	945 (15.1)	3437 (16.6)	466 (15.0)
9 or 10 (most deprived)	393 (15.7)	747 (11.9)	2491 (12.0)	337 (10.8)
<b>Housebound</b>	101 (4.0)	251 (4.0)	641 (3.1)	107 (3.4)
<b>Respiratory disease</b>	478 (19.1)	1159 (18.5)	3934 (19.0)	629 (20.2)
<b>Cardiac failure</b>	178 (7.1)	438 (7.0)	1365 (6.6)	202 (6.5)
<b>Dementia</b>	160 (6.4)	399 (6.4)	1080 (5.2)	158 (5.1)
<b>Peripheral vascular disease</b>	218 (8.7)	573 (9.2)	1695 (8.2)	248 (8.0)
<b>Renal disease</b>	620 (24.8)	1560 (24.9)	4758 (23.0)	755 (24.3)
<b>Rheumatoid arthritis</b>	47 (1.9)	105 (1.7)	374 (1.8)	53 (1.7)
<b>Cancer</b>	486 (19.5)	1306 (20.9)	4225 (20.4)	689 (22.1)
<b>Stroke</b>	320 (12.8)	856 (13.7)	2542 (12.3)	370 (11.9)
<b>Diabetes</b>	576 (23.1)	1411 (22.6)	4659 (22.5)	677 (21.8)
<b>Liver disease</b>	17 (0.7)	36 (0.6)	122 (0.6)	23 (0.7)
<b>Ischaemic heart disease</b>	674 (27.0)	1622 (25.9)	5347 (25.8)	811 (26.1)
<b>Urinary catheter</b>	182 (7.3)	626 (10.0)	1783 (8.6)	325 (10.4)
<b>Urinary incontinence</b>	184 (7.4)	496 (7.9)	1393 (6.7)	225 (7.2)
<b>Polypharmacy</b>	1048 (42.0)	2462 (39.4)	7859 (37.9)	1123 (36.1)
<b>Benign prostatic hyperplasia</b>	760 (30.4)	1953 (31.2)	6341 (30.6)	1033 (33.2)
<b>Prostate cancer</b>	213 (8.5)	626 (10.0)	2071 (10.0)	331 (10.6)
<b>eGFR</b>				
60-90	1569 (62.8)	3909 (62.5)	13573 (65.5)	2016 (64.8)
45-59	514 (20.6)	1269 (20.3)	4101 (19.8)	600 (19.3)
30-44	223 (8.9)	563 (9.0)	1735 (8.4)	280 (9.0)
15-29	69 (2.8)	201 (3.2)	478 (2.3)	93 (3.0)
<15	19 (0.8)	48 (0.8)	74 (0.4)	11 (0.4)
missing	104 (4.2)	264 (4.2)	768 (3.7)	112 (3.6)

<b>Charlson score</b>				
0	657 (26.3)	1594 (25.5)	5819 (28.1)	836 (26.9)
1	484 (19.4)	1254 (20.1)	4067 (19.6)	579 (18.6)
2	512 (20.5)	1230 (19.7)	3958 (19.1)	613 (19.7)
3	334 (13.4)	902 (14.4)	2881 (13.9)	450 (14.5)
4	219 (8.8)	522 (8.3)	1759 (8.5)	258 (8.3)
5	141 (5.6)	351 (5.6)	1131 (5.5)	189 (6.1)
≥6	151 (6.0)	401 (6.4)	1114 (5.4)	187 (6.0)

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Table 2. Adjusted ORs and 95% CIs for each outcome by antibiotic prescription duration.

<b>Re-consultation and re-prescription within 14 days</b>	<b>Number of prescriptions</b>	<b>Number (%) of events</b>	<b>Crude OR</b>	<b>Adjusted OR (95% CI)</b>	<b>p-value</b>
7 days [reference]	20729	1225 (5.9)	1	1	
3 days	2498	198 (7.9)	1.37	1.48 (1.25 - 1.74)	<0.001
5 days	6254	416 (6.7)	1.13	1.18 (1.04 - 1.33)	0.009
8-14 days	3112	168 (5.4)	0.91	0.80 (0.67 - 0.96)	0.020
<b>Hospitalised for UTI within 14 days</b>					
7 days [reference]	20729	543 (2.6)	1	1	
3 days	2498	61 (2.4)	0.93	0.87 (0.66 - 1.15)	0.331
5 days	6254	147 (2.4)	0.89	0.82 (0.67 - 1.01)	0.063
8-14 days	3112	66 (2.1)	0.81	0.81 (0.61 - 1.08)	0.152
<b>Hospitalised for sepsis within 14 days</b>					
7 days [reference]	20729	53 (0.3)	1	1	
3 days	2498	4 (0.2)	0.63	0.63 (0.22 - 1.75)	0.366
5 days	6254	13 (0.2)	0.81	0.63 (0.34 - 1.19)	0.159
8-14 days	3112	9 (0.3)	1.13	0.85 (0.38 - 1.90)	0.700
<b>Hospitalised for AKI within 14 days</b>					
7 days [reference]	20729	307 (1.5)	1	1	
3 days	2498	30 (1.2)	0.82	0.66 (0.45 - 0.97)	0.033
5 days	6254	88 (1.4)	0.97	0.84 (0.66 - 1.08)	0.182
8-14 days	3112	24 (0.8)	0.53	0.63 (0.40 - 0.99)	0.047
<b>Death within 28 days</b>					
7 days [reference]	20729	252 (1.2)	1	1	
3 days	2498	37 (1.5)	1.22	1.12 (0.78 - 1.61)	0.522
5 days	6254	89 (1.4)	1.17	1.01 (0.78 - 1.31)	0.917
8-14 days	3112	41 (1.3)	1.08	1.21 (0.83 - 1.78)	0.316

Table 3. Baseline characteristics before and after propensity-score matching of men prescribed three versus seven days of antibiotics. Values are numbers (%) unless otherwise stated. \*SMD = standardised mean difference

	Before matching			After matching		
	3 days	7 days	SMD*	3 days	7 days	SMD*
<b>Number (%) of prescriptions</b>	2498 (7.7)	20729 (63.6)		2394 (25.0)	7182 (75.0)	
<b>Mean (SD) age</b>	77.4 (8.0)	76.9 (7.9)	0.071	77.5 (8.0)	77.4 (8.0)	0.008
<b>Antibiotic choice</b>						
Amoxicillin	12 (0.5)	1392 (6.7)	-0.887	12 (0.5)	39 (0.5)	-0.006
Cefalexin	60 (2.4)	1133 (5.5)	-0.202	57 (2.4)	166 (2.3)	0.005
Ciprofloxacin	38 (1.5)	649 (3.1)	-0.127	38 (1.6)	109 (1.5)	0.006
Co-amoxiclav	13 (0.5)	1843 (8.9)	-1.141	13 (0.5)	36 (0.5)	0.006
Nitrofurantoin	241 (9.6)	3301 (16.0)	-0.217	231 (9.6)	703 (9.8)	-0.005
Trimethoprim	2134 (85.4)	12411 (60.0)	0.727	2043 (85.3)	6129 (85.3)	0.000
<b>IMD decile</b>						
1 or 2 (least deprived)	527 (21.1)	5217 (25.2)		498 (20.8)	1497 (20.8)	
3 or 4	552 (22.1)	5016 (24.2)		529 (22.1)	1545 (21.5)	
5 or 6	599 (24.0)	4568 (22.0)		578 (24.1)	1703 (23.7)	
7 or 8	427 (17.1)	3437 (16.6)		408 (17.0)	1368 (19.0)	
9 or 10 (most deprived)	393 (15.7)	2491 (12.0)	0.147	381 (15.9)	1069 (14.9)	0.000
<b>Housebound</b>	101 (4.0)	641 (3.1)	0.052	100 (4.2)	296 (4.1)	0.003
<b>Respiratory disease</b>	478 (19.1)	3934 (19.0)	0.002	460 (19.2)	1371 (19.1)	0.003
<b>Cardiac failure</b>	178 (7.1)	1365 (6.6)	0.025	178 (7.4)	527 (7.3)	0.004
<b>Dementia</b>	160 (6.4)	1080 (5.2)	0.044	151 (6.3)	469 (6.5)	-0.009
<b>Peripheral vascular disease</b>	218 (8.7)	1695 (8.2)	0.018	213 (8.9)	622 (8.7)	0.008
<b>Renal disease</b>	620 (24.8)	4758 (23.0)	0.047	618 (25.8)	1764 (24.6)	0.029
<b>Rheumatoid arthritis</b>	47 (1.9)	374 (1.8)	-0.002	44 (1.8)	129 (1.8)	0.003
<b>Cancer</b>	486 (19.5)	4225 (20.4)	-0.022	476 (19.9)	1408 (19.6)	0.007
<b>Stroke</b>	320 (12.8)	2542 (12.3)	0.023	319 (13.3)	935 (13.0)	0.009
<b>Diabetes</b>	576 (23.1)	4659 (22.5)	0.020	576 (24.1)	1692 (23.6)	0.012
<b>Liver disease</b>	17 (0.7)	122 (0.6)	0.016	17 (0.7)	51 (0.7)	0.000
<b>Ischaemic heart disease</b>	674 (27.0)	5347 (25.8)	0.028	667 (27.9)	1983 (27.6)	0.006
<b>Urinary catheter</b>	182 (7.3)	1783 (8.6)	-0.053	174 (7.3)	498 (6.9)	0.013
<b>Urinary incontinence</b>	184 (7.4)	1393 (6.7)	0.018	175 (7.3)	512 (7.1)	0.007
<b>Polypharmacy</b>	1048 (42.0)	7859 (37.9)	0.086	1033 (43.1)	3080 (42.9)	0.005
<b>Prostatic hyperplasia</b>	760 (30.4)	6341 (30.6)	-0.006	743 (31.0)	2138 (29.8)	0.027
<b>Prostate cancer</b>	213 (8.5)	2071 (10.0)	-0.056	207 (8.6)	618 (8.6)	0.002
<b>eGFR</b>						
60-90	1569 (62.8)	13573 (65.5)		1569 (65.5)	4740 (66)	
45-59	514 (20.6)	4101 (19.8)		514 (21.5)	1558 (21.7)	
30-44	223 (8.9)	1735 (8.4)		223 (9.3)	685 (9.5)	
15-29	69 (2.8)	478 (2.3)		69 (2.9)	172 (2.4)	
<15	19 (0.8)	74 (0.4)		19 (0.8)	27 (0.4)	
missing	104 (4.2)	768 (3.7)	0.064	0 (0)	0 (0)	0.029
<b>Charlson score</b>						
0	657 (26.3)	5819 (28.1)		594 (24.8)	1894 (26.4)	
1	484 (19.4)	4067 (19.6)		463 (19.3)	1385 (19.3)	
2	512 (20.5)	3958 (19.1)		499 (20.8)	1423 (19.8)	
3	334 (13.4)	2881 (13.9)		328 (13.7)	1003 (14)	
4	219 (8.8)	1759 (8.5)		218 (9.1)	623 (8.7)	
5	141 (5.6)	1131 (5.5)		141 (5.9)	425 (5.9)	
≥6	151 (6.0)	1114 (5.4)	0.045	151 (6.3)	429 (6.0)	0.027

Table 4. Odds ratios and 95% CIs for each outcome in men matched on their propensity to receive a seven-day antibiotic prescription.

	<b>7 day prescriptions</b>	<b>3 day prescriptions</b>		
<b>Outcome</b>	<b>Number (%) of events</b>	<b>Number (%) of events</b>	<b>OR (95% CI)*</b>	<b>p-value</b>
<b>Re-consultation and re-prescription within 14 days</b>	399 (5.6)	192 (8.0)	1.52 (1.25 - 1.85)	<0.001
<b>Hospitalised for UTI within 14 days</b>	209 (2.9)	59 (2.5)	0.81 (0.61 - 1.09)	0.179
<b>Hospitalised for sepsis within 14 days</b>	18 (0.3)	4 (0.2)	0.60 (0.20 - 1.75)	0.350
<b>Hospitalised for AKI within 14 days</b>	131 (1.8)	29 (1.2)	0.62 (0.42 - 0.93)	0.021
<b>Death within 28 days</b>	96 (1.3)	36 (1.5)	1.07 (0.73 - 1.57)	0.729

\*Reference = 7 day prescription

## Figure legends

Figure 1. Flow of men from initial identification in the database to final cohort.

## Figures

Figure 1.

