

Antibiotic prophylaxis and clinical outcomes among older adults with recurrent urinary tract infection: cohort study

Abstract

Background

Clinical guidelines recommend antibiotic prophylaxis for preventing recurrent urinary tract infections (UTIs), but there is little evidence for their effectiveness in older adults.

Methods

This was a retrospective cohort study of health records from 19,696 adults aged ≥ 65 with recurrent UTIs. We used prescription records to ascertain ≥ 3 months' prophylaxis with trimethoprim, cefalexin or nitrofurantoin. We used random effects Cox recurrent event models to estimate hazard ratios (HR) and 95% confidence intervals (CI) for risks of clinical recurrence (primary outcome), acute antibiotic prescribing, and hospitalisation.

Results

Of 4043 men and 15,653 women aged ≥ 65 with recurrent UTIs, 508 men (12.6%) and 2229 women (14.2%) were prescribed antibiotic prophylaxis. In men, prophylaxis was associated with a reduced risk of clinical recurrence (HR, 0.49; 95% CI, 0.45-0.54), acute antibiotic prescribing (HR, 0.54; 95% CI, 0.51-0.57) and UTI-related hospitalisation (HR, 0.78; 95% CI, 0.64–0.94). In women, prophylaxis was also associated with a reduced risk of clinical recurrence (HR, 0.57; 95% CI, 0.55-0.59) and acute antibiotic prescribing (HR, 0.61; 95% CI, 0.59-0.62), but estimates of the risk of UTI-related hospitalisation were inconsistent between our main analysis (HR, 1.16; 95% CI, 1.05-1.28) and sensitivity analysis (HR, 0.82; 95% CI, 0.72-0.94).

Conclusions

Antibiotic prophylaxis was associated with lower rates of UTI recurrence and acute antibiotic prescribing in older adults. To fully understand the benefits and harms of prophylaxis, further research should determine the frequency of antibiotic-related adverse events and the impact on antimicrobial resistance and quality of life.

Key Words

Urinary tract infection

Antibiotic prophylaxis

Recurrence

Older adults

Key Points

- This is the first study to provide robust data to inform the use of antibiotic prophylaxis in older men with recurrent UTI, and estimate risk of clinical outcomes in an unselected real-world cohort of older adults with recurrent UTI.
- Antibiotic prophylaxis was associated with a 51% reduction in risk of UTI recurrence in older men, and a 43% reduction in older women.
- Antibiotic prophylaxis was associated with a 22% reduction in risk of UTI-related hospitalisation in older men, but risk estimates in older women were inconsistent across different analyses and warrant further investigation.

Main Text

Introduction

Urinary tract infections (UTI) affected 150 million people in 2015. [1] In the UK, between 2001 and 2011, hospital admission for UTI doubled, accounting for an additional £369 million in health service costs. [2] Most of this increase is attributable to adults aged 65 and over, [3] and thus there is considerable interest in evaluating methods of preventing UTIs in older people. Prophylactic antibiotics are widely prescribed to care home residents to prevent recurrent UTIs, defined as three or more UTIs in a year, or two or more in six months. [4-6] Clinical guidelines recommend several methods for preventing recurrent UTIs including avoidance of risk factors, vaginal oestrogens, immunoprophylaxis, or long-term low-dose antibiotic prophylaxis. [7, 8]

Our systematic review and meta-analysis of randomised trials identified a reduction in risk of UTI recurrence in post-menopausal women prescribed antibiotic prophylaxis compared to those prescribed non-antibiotic prophylaxis during 6-12 months of follow-up. [9] However, the existing evidence has several gaps and limitations. Firstly, there are no robust data to inform prophylactic antibiotic use in men. Secondly, trials in post-menopausal women often excluded those with co-morbidities such as diabetes, thus limiting their generalizability. Thirdly, previous studies were underpowered to study important but rare events such as hospitalisation.

A randomised trial could address some of these issues but there would be significant challenges, including recruitment and retention of older adults into a clinical trial with long-term follow-up, [10] and associated costs and time scales. Epidemiological analyses of routinely collected healthcare data provide an opportunity to generate

clinically useful evidence efficiently and cost-effectively. Therefore, we analysed data from anonymised linked health records of older adults with recurrent UTI to investigate gender-specific associations between antibiotic prophylaxis and clinical outcomes, including hospitalisation, whilst accounting for comorbidities.

Methods

Data Source

We used the Clinical Practice Research Datalink (CPRD), an electronic database of anonymised primary care records, covering 11.3 million patients from 674 general practices across the UK.[11] Approximately 7% of the UK population are included and patients are broadly representative of the wider UK population in terms of age, gender and ethnicity. The CPRD holds data on demographics, clinical encounters and diagnoses (coded using Read codes), drug prescriptions, laboratory tests and referrals to specialists. Data are available once they have met a series of quality checks on completeness and reliability and the CPRD deems them to be of a required standard for research purposes. Linked hospital data is available for patients from approximately 50% of contributing English practices. Hospital diagnoses are recorded using version 10 of the International Classification of Disease (ICD-10).

Design and participants

This was a retrospective cohort study using linked health record data. Patients were eligible for inclusion if, between 1st March 2004 and 31st December 2015, their data were of the quality required by CPRD, they were ≥ 65 years old, had linked hospital admission data, and met the definition of recurrent UTI of ≥ 3 incident UTIs in a year. UTIs were identified using Read codes recorded by primary care clinicians or ICD-10

codes recorded in hospital admission data (See Appendix 1 in the supplementary material). To account for multiple consultations for the same illness episode, we considered UTI-related codes occurring within a 28-day period to belong to the same episode. To ensure we only included *community-acquired* UTI, we considered UTI episodes within 14 days of a hospital discharge to be hospital-acquired and excluded these. We excluded patients if they were temporary residents or had periods of time for which CPRD was unable to collect their health record data. We also excluded those who had commenced antibiotic prophylaxis prior to meeting the definition of recurrent UTI, those who met the definition of recurrent UTI but were prescribed prophylaxis with an antibiotic other than those of interest to this study, and those with a prophylaxis period of less than three months.

Exposure

The exposure of interest was prescription records indicating at least three consecutive months prescribing of trimethoprim, nitrofurantoin or cefalexin. These were the only antibiotics recommended for UTI prophylaxis by the British National Formulary (BNF) during the study period, and long-term prescribing was not indicated for other conditions. Therefore, in this cohort of individuals with recurrent UTIs, it is likely that long-term prescribing was for UTI prophylaxis.

To investigate associations between antibiotic prophylaxis and outcomes, we partitioned patients' follow-up times into unexposed and exposed periods (Figure 2 in supplementary material). Unexposed periods began from the day the patient met the definition of recurrent UTI to the earliest of, day of their first prophylactic antibiotic prescription, study end date (31st December 2015), death, or last day of available CPRD data. Exposed periods began from day of their first prophylactic antibiotic

prescription to the earliest of, study end date (31st December 2015), death, or last day of available CPRD data. We regarded patients as exposed to prophylactic antibiotics from the day of their first prescription to the end of their follow-up. We estimated risk of each outcome during exposed versus unexposed periods.

Outcomes

The primary outcome was clinical recurrence, defined as a primary care record of symptoms or diagnoses indicating a UTI and a same-day acute antibiotic prescription. Relevant symptoms and diagnoses were identified using codes from code list 1 in supplementary appendix 1, the most common being “dysuria”, “frequency of micturition”, “urinary symptoms”, “urinary tract infection”, and “acute cystitis”. Secondary outcomes were all-cause primary care acute antibiotic prescribing, with one prescription equal to one event, UTI-related hospitalisation, ascertained from linked hospital data using relevant ICD-10 codes (codes N30.0, N30.9, N39.0), and all-cause (emergency and elective) hospitalisation.

Statistical Analyses

We used primary care demographic and clinical codes to describe baseline characteristics by exposure status. We used random effects Cox recurrent event models to estimate hazard ratios and 95% confidence intervals for each outcome, and used a shared frailty term to account for clustering of multiple correlated events within individuals. This approach introduces a random covariate into the model that induces dependence among the recurrent event times, and describes the excess risk for distinct individuals whilst accounting for unmeasured heterogeneity that remains unexplained using observed covariates alone. [12-14]

We adjusted for age, index of multiple deprivation score quintile, the presence or absence of a record indicating; diabetes, dementia, coronary heart disease, renal disease, stroke, cancer, heart failure, urinary incontinence and urinary catheter; polypharmacy, (defined as records indicating ≥ 5 long-term medications per months in the year prior to cohort entry), and a Charlson comorbidity score. [15]

We did several sensitivity analyses. Firstly, to assess robustness of associations between antibiotic prophylaxis and outcomes, we used data on time between prescriptions, number of tablets issued and prescribed dosage instructions to split exposed periods into “consistent exposure”, “inconsistent exposure” (proxies for compliance) and “post-exposure” periods and estimated risk of outcome for each period, with the unexposed period as the reference. Secondly, we selected only those patients with an unexposed *and* an exposed period and estimated risk of outcomes using a self-controlled case series design where each patient’s unexposed period acted as their own control, thus reducing bias from between person residual confounding. Finally, we explored the impact of prophylactic dose and duration.

Analyses were conducted in R version 3.2.1.

Results

There were 966,454 patients aged ≥ 65 between 2004 and 2015 with data of the required quality and with linked hospital data, in the database. Of these, 931,945 (96%) met our initial eligibility criteria, and 25,276 (2.7%) had clinical records indicating recurrent UTI. Following further exclusions (Figure 1 in supplementary material), we entered 19,696 patients from 393 primary care practices into our final cohort. 2737 (13.9%) of these patients had a period of exposure to antibiotic prophylaxis for recurrent UTI, of whom 508 (18.6%) were men.

Baseline characteristics

Baseline characteristics were mostly similar for patients prescribed versus not prescribed antibiotic prophylaxis, except for higher proportions of patients with urinary incontinence and polypharmacy in the prophylaxis group (Table 1).

Trimethoprim was the most commonly prescribed prophylactic antibiotic (Table 2).

Over 20% of prophylactic antibiotic prescriptions were for a dose greater than that recommended for UTI prophylaxis by the BNF. Almost 50% of patients were prescribed prophylactic antibiotics for over two years.

Antibiotic prophylaxis and risk of each outcome

Of 4043 men, 2750 men had 10,722 clinical recurrences, with 9387 recurrences during unexposed periods and 1335 recurrences during exposed periods (Table 3).

Antibiotic prophylaxis was associated with a significantly lower risk of clinical recurrence (adjusted HR, 0.49; 95% CI, 0.45-0.54), acute antibiotic prescribing (adjusted HR, 0.54; 95% CI, 0.51-0.57), and UTI-related hospitalisation (adjusted HR, 0.78; 95% CI, 0.64-0.94). We found no significant association between antibiotic prophylaxis and all-cause hospitalisation. Risk estimates were consistent across all sensitivity analyses (Table 1 in the supplementary material).

Of 15,653 women, 11,845 women had 60,124 clinical recurrences, with 51,748 recurrences during unexposed periods and 8376 recurrences during exposed periods. Antibiotic prophylaxis was associated with a significantly lower risk of clinical recurrence (adjusted HR, 0.57; 95% CI, 0.55-0.59), and acute antibiotic prescribing (adjusted HR, 0.61; 95% CI, 0.59-0.62). These estimates were consistent across all sensitivity analyses. Antibiotic prophylaxis was associated with an increased risk of UTI-related hospitalisation in our main analysis (adjusted HR, 1.19; 95% CI, 1.08-

1.31). However, when we re-assessed the risk using a self-controlled case series design, the direction of effect reversed (adjusted HR, 0.82; 95% CI, 0.72-0.94) (Table 2 in the supplementary material). We found no significant association between antibiotic prophylaxis and all-cause hospitalisation in our main analysis, but found an 8% risk increase in our self-controlled case series analysis (adjusted HR, 1.08; 95% CI 1.02-1.15).

In men and women, clinical recurrence rates were similar among those prescribed prophylaxis for ≤ 6 months (reference group), 7-12 months, 13-18 months, and 19-24 months, but were lower for those prescribed prophylaxis for >24 months (HR, 0.77; 95% CI 0.65-0.90). Restricting the analyses to those prescribed the correct prophylaxis dose had little impact on risk estimates.

Discussion

Summary of main findings

We found reduced risks of clinical recurrence and acute antibiotic prescribing for older men and women with recurrent UTI during periods of prophylactic antibiotic exposure. There was also a reduced risk of UTI-related hospitalisation in older men. These associations were consistent across several sensitivity analyses. We found an unexpected increased risk of UTI-related hospitalisation for women associated with exposure to prophylactic antibiotics, although the direction of effect reversed in our analysis that used individuals as their own controls. We therefore hypothesise that this inconsistent finding is due to residual unmeasured confounding that was unaccounted for in the main analyses. For example, women who received prophylaxis may have been less healthy than women who did not receive prophylaxis and thus at increased risk of hospitalisation irrespective of exposure.

This may also explain the inconsistencies between findings for antibiotic exposure and all-cause hospitalisation in women. Given the observed inconsistencies in risk estimates, these findings warrant further investigation.

Comparison with other studies

To our knowledge, there are no rigorous randomised trials or observational studies investigating the effect of antibiotic prophylaxis in older men with recurrent UTI. One previous observational study found that around 13% of older men who experienced a UTI had at least one recurrence. [16] Our analyses showed that only 13% of older men with recurrent UTI were prescribed antibiotic prophylaxis, but those that were had significantly lower rates of clinical recurrence, UTI-related hospitalisation and acute antibiotic prescribing. The low prescribing rates are likely due to male UTI being considered a more complicated infection and thus reluctance to prescribe until serious causes have been excluded, and also due to the dearth of empirical data to inform clinical practice.

Our finding of reduced risk of clinical recurrence for older women prescribed prophylactic antibiotics is consistent with findings from meta-analyses of post-menopausal women [9] and younger women.[17] Clinical guidelines, recommend long-term antibiotic prophylaxis for women with recurrent UTI, [7, 8] but only 14% of older women in our sample were prescribed antibiotic prophylaxis, suggesting scope for further benefit through better implementation of clinical guidelines.

Strengths and limitations

To our knowledge, this study is the first to provide robust data to inform the use of antibiotic prophylaxis in older men with recurrent UTI and estimate risk of important clinical outcomes, including hospitalisation, in an unselected, real-world cohort of

older adults with recurrent UTI. This is a large study based on a representative sample of older people with over 60,000 person years of follow-up. We used a strict definition of three clinically recorded incident UTI episodes in one year to define eligibility and limit indication bias. Clinical trials used self-report,[18] primary care records, [19] or were unclear about how they identified patients with a history of recurrent UTI. [20, 21] Similar to previous database research on infections, we used Read and ICD-10 codes to identify UTI episodes and made allowances to distinguish repeat consultations for the same episode from incident episodes. [22, 23] We used primary care records to ascertain exposure to antibiotic prophylaxis. Recording of prescriptions issued in UK primary care has high levels of completeness, thus representing an accurate and reliable source of exposure data. [24] We used clinically recorded diagnoses to adjust for a range of co-morbid conditions with previous research suggesting these are reliably coded in primary care records. [25]

A limitation of our study is the use of clinical recurrence rather than microbiologically confirmed recurrence as the primary outcome. The main reason for this is that the CPRD does not contain microbiological data but, even if it did, urine sampling in UK primary care is highly variable and therefore less useful in a retrospective study. The lack of microbiology data also meant we were unable to investigate any impact on urinary bacterial antibiotic resistance. Our exposure data represented antibiotic prescribing, not antibiotic use. We were unable to investigate antibiotic related adverse events. A wide variety of codes could be used to record these events and it is difficult to reliably associate these codes with the prescribed antibiotic without a more detailed account of the clinical scenario.

Implications

Our findings show that antibiotic prophylaxis is associated with reduced clinical recurrence and acute antibiotic prescribing in older men and women with recurrent UTI. These findings support those from randomised trials of older women, and provide the only robust data currently available to inform clinical practice for older men. The NICE Quality Standards for UTI in adults highlights the lack of clinical guidance for management of recurrent UTI.[26] Although our data showed some associated benefit, overall, the ongoing uncertainties around the risk of hospitalisation in women, the rate of antibiotic-related adverse events, and the impact on antimicrobial resistance, mean that further research is needed to fully understand the risks and benefits of antibiotic prophylaxis in recurrent UTI.

Conflicts of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Tables

Table 1. Characteristics of individuals with recurrent UTI prescribed prophylactic antibiotics versus those not prescribed prophylactic antibiotics. Values are numbers (%) unless otherwise stated.

Characteristics	Patients prescribed prophylactic antibiotics	Patients not prescribed prophylactic antibiotics
Total	2737	16959
Male	508 (18.6)	3535 (20.8)
Median (IQR) age at cohort entry	77.3 (71.4 – 84.0)	78.7 (72.3 – 85.1)
Median (IQR) follow-up time in days	1546 (877-2403)	826 (322-1650.5)
2010 English Index of multiple deprivation quintile:		
1 (least deprived)	661 (24.2)	3936 (23.2)
2	738 (27.0)	4441 (26.2)
3	606 (22.1)	3641 (21.5)
4	427 (15.6)	2876 (17.0)
5 (most deprived)	303 (11.1)	2048 (12.0)
missing	2 (0)	17 (0.1)
Housebound	108 (3.9)	816 (4.8)
Dementia	204 (7.4)	1268 (7.5)
Diabetes	475 (17.4)	2951 (17.4)
Coronary heart disease	587 (21.4)	3635 (21.4)
Congestive cardiac failure	130 (4.7)	1159 (6.8)
Renal Disease	492 (18.0)	3454 (20.4)
Stroke	344 (12.6)	2208 (13.0)
Urinary incontinence	630 (23.0)	3379 (19.9)
Urinary Catheter	198 (7.2)	1248 (7.4)
Polypharmacy	1203 (44.0)	6935 (40.9)
eGFR:		
>90	156 (5.7)	1096 (6.5)
60-90	1101 (40.2)	6508 (38.4)
45-59	719 (26.3)	4547 (26.8)
30-44	362 (13.2)	2042 (12.0)
15-29	62 (2.3)	500 (2.9)
<15	6 (0.2)	74 (0.4)
missing	331 (12.1)	2192 (12.9)
Charlson score:		
0	887 (32.4)	5241 (30.9)
1	670 (24.5)	3804 (22.4)
2	488 (17.8)	3294 (19.4)
3	328 (12.0)	2122 (12.5)
4	179 (6.5)	1176 (6.9)
5	101 (3.7)	640 (3.8)
≥6	84 (3.1)	682 (4.0)

Table 2. Initial choice, dose and duration of prophylactic antibiotics. Values are numbers (%) unless otherwise stated.

	Men (n=508)	Women (n=2229)
Choice:		
Trimethoprim	282 (55.5)	1009 (45.3)
Nitrofurantoin	160 (31.5)	811 (36.4)
Cephalexin	66 (13.0)	409 (18.3)
Daily dose:		
As per BNF recommended dose	240 (47.2)	1104 (49.5)
Below recommended dose	0 (0)	2 (0.1)
Above recommended dose	109 (21.5)	498 (22.3)
Unable to calculate daily dose	159 (31.3)	625 (28.0)
Duration of treatment:		
3 months	5 (1.0)	17 (0.8)
4-6 months	53 (10.4)	217 (9.7)
7-12 months	102 (20.1)	355 (15.9)
13-18 months	70 (13.8)	320 (14.4)
19-24 months	57 (11.2)	214 (9.6)
>24 months	221 (43.5)	1106 (49.6)

Table 3. Number of events, person years of follow-up, and adjusted hazard ratios for each outcome.

Outcomes in men	Events	Person years	Rate*	Crude HR	Adjusted HR (95% CI)	P value
Clinical recurrence						
Unexposed	9387	9271	101.25	R	R	R
Exposed	1335	1446	92.31	0.47	0.49 (0.45 - 0.54)	<0.001
UTI related hospitalisation						
Unexposed	1684	9271	18.16	R	R	R
Exposed	233	1446	16.11	0.77	0.78 (0.64 - 0.94)	0.014
All-cause acute antibiotic prescribing						
Unexposed	27959	9271	301.57	R	R	R
Exposed	4048	1446	279.91	0.53	0.54 (0.51 - 0.57)	<0.001
All-cause hospitalisation						
Unexposed	14714	9271	158.71	R	R	R
Exposed	1879	1446	129.93	0.90	0.93 (0.85 - 1.01)	0.080
Outcomes in women						
Clinical recurrence						
Unexposed	51748	44385	116.59	R	R	R
Exposed	8376	7244	115.62	0.55	0.57 (0.55 - 0.59)	<0.001
UTI related hospitalisation						
Unexposed	4314	44385	9.72	R	R	R
Exposed	999	7244	13.79	1.14	1.16 (1.05 - 1.28)	0.002
All-cause acute antibiotic prescribing						
Unexposed	134860	44385	303.84	R	R	R
Exposed	23025	7244	317.83	0.60	0.61 (0.59 - 0.62)	<0.001
All-cause hospitalisation						
Unexposed	38705	44385	87.20	R	R	R
Exposed	5935	7244	81.93	1.05	1.03 (0.98 - 1.08)	0.210

*rate is per 100 person years.

Supplementary Table 1. Number of events, person years of follow-up and adjusted hazard ratios for main and sensitivity analyses in men.

									SELF-CONTROLLED CASE SERIES ANALYSES						
OUTCOMES IN MEN	EVENTS	PERSON YEARS	RATE ^a	CRUDE HR	ADJUSTED HR	LCI ^b	UCI ^c	P value	EVENTS	PERSON YEARS	RATE ^a	ADJUSTED HR	LCI ^b	UCI ^c	P value
CLINICAL RECURRENCE															
Unexposed periods	9387	9271.01	101.25	R	R	R	R	R	1563	514.74	303.65	R	R	R	R
Exposed periods (main analysis)	1335	1446.17	92.31	0.47	0.49	0.45	0.54	<.001	1335	1446.17	92.31	0.31	0.28	0.34	<0.001
Consistent exposure periods	964	981.96	98.17	0.50	0.51	0.47	0.56	<.001							
Inconsistent exposure periods	161	179.94	89.47	0.37	0.42	0.34	0.51	<.001							
Post-exposure periods	210	284.27	73.87	0.38	0.45	0.38	0.53	<.001							
UTI RELATED HOSPITALISATION															
Unexposed periods	1684	9271.01	18.16	R	R	R	R	R	139	514.74	27.00	R	R	R	R
Exposed periods (main analysis)	233	1446.17	16.11	0.77	0.78	0.64	0.94	0.01	233	1446.17	16.11	0.60	0.46	0.79	<0.001
Consistent exposure periods	156	981.96	15.89	0.75	0.74	0.59	0.92	0.01							
Inconsistent exposure periods	26	179.94	14.45	0.74	0.80	0.50	1.29	0.38							
Post-exposure periods	51	284.27	17.94	0.82	0.92	0.64	1.32	0.78							
ALL-CAUSE ACUTE ANTIBIOTIC PRESCRIBING															
Unexposed periods	27959	9271.01	301.57	R	R	R	R	R	3387	514.74	658.01	R	R	R	R
Exposed periods (main analysis)	4048	1446.17	279.91	0.53	0.54	0.51	0.57	<0.001	4048	1446.17	279.91	0.40	0.38	0.43	<0.001
Consistent exposure periods	2876	981.96	292.88	0.55	0.55	0.52	0.58	<0.001							
Inconsistent exposure periods	492	179.94	273.42	0.47	0.49	0.43	0.55	<0.001							
Post-exposure periods	680	284.27	239.21	0.51	0.54	0.49	0.60	<0.001							
ALL-CAUSE HOSPITALISATION															
Unexposed periods	14714	9271.01	158.71	R	R	R	R	R	744	514.74	144.54	R	R	R	R
Exposed periods (main analysis)	1879	1446.17	129.93	0.90	0.93	0.85	1.01	0.08	1879	1446.17	129.93	0.98	0.88	1.10	0.75
Consistent exposure periods	1323	981.96	134.73	0.93	0.92	0.84	1.01	0.08							
Inconsistent exposure periods	164	179.94	91.14	0.72	0.84	0.68	1.03	0.09							
Post-exposure periods	392	284.27	137.90	0.90	1.01	0.87	1.18	0.87							

Supplementary Table 2. Number of events, person years of follow-up and adjusted hazard ratios for main and sensitivity analyses in women.

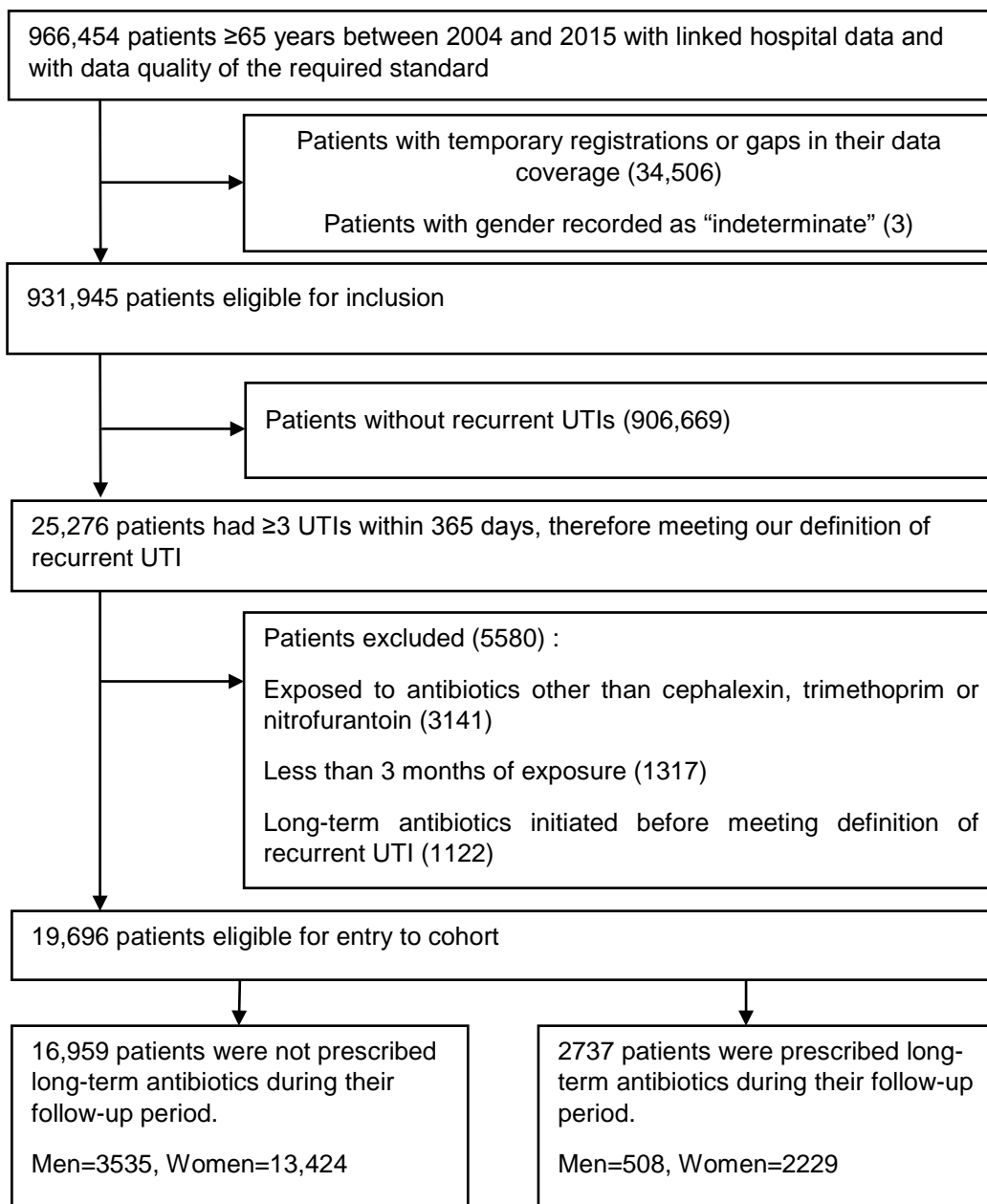
									SELF-CONTROLLED CASE SERIES ANALYSES						
OUTCOMES IN WOMEN	EVENTS	PERSON YEARS	RATE ^a	CRUDE HR	ADJUSTED HR	LCI ^b	UCI ^c	P value	EVENTS	PERSON YEARS	RATE ^a	ADJUSTED HR	LCI ^b	UCI ^c	P value
CLINICAL RECURRENCE															
Unexposed periods	51748	44385.23	116.59	R	R	R	R	R	9753	3423.50	284.88	R	R	R	R
Exposed periods (main analysis)	8376	7244.39	115.62	0.55	0.57	0.55	0.59	<.001	8376	7244.39	115.62	0.34	0.33	0.36	<0.001
Consistent exposure periods	5298	4683.67	113.12	0.55	0.56	0.54	0.58	<.001							
Inconsistent exposure periods	1719	1229.40	139.82	0.59	0.64	0.60	0.69	<.001							
Post-exposure periods	1359	1331.32	102.08	0.52	0.58	0.54	0.62	<.001							
UTI RELATED HOSPITALISATION															
Unexposed periods	4314	44385.23	9.72	R	R	R	R	R	565	3423.50	16.50	R	R	R	R
Exposed periods (main analysis)	999	7244.39	13.79	1.14	1.16	1.05	1.28	0.00	999	7244.39	13.79	0.82	0.72	0.94	0.005
Consistent exposure periods	606	4683.67	12.94	1.15	1.13	1.02	1.26	0.02							
Inconsistent exposure periods	172	1229.40	13.99	1.06	1.13	0.92	1.37	0.25							
Post-exposure periods	221	1331.32	16.60	1.20	1.29	1.09	1.53	0.00							
ALL-CAUSE ACUTE ANTIBIOTIC PRESCRIBING															
Unexposed periods	134860	44385.23	303.84	R	R	R	R	R	20647	3423.50	603.10	R	R	R	R
Exposed periods (main analysis)	23025	7244.39	317.83	0.60	0.61	0.59	0.62	<0.001	23025	7244.39	317.83	0.44	0.43	0.45	<0.001
Consistent exposure periods	14482	4683.67	309.20	0.59	0.60	0.58	0.61	<0.001							
Inconsistent exposure periods	4506	1229.40	366.52	0.61	0.63	0.60	0.66	<0.001							
Post-exposure periods	4037	1331.32	303.23	0.60	0.63	0.60	0.65	<0.001							
ALL-CAUSE HOSPITALISATION															
Unexposed periods	38705	44385.23	87.20	R	R	R	R	R	2898	3423.50	84.65	R	R	R	R
Exposed periods (main analysis)	5935	7244.39	81.93	1.05	1.03	0.98	1.08	0.21	5935	7244.39	81.93	1.08	1.02	1.15	0.013
Consistent exposure periods	3593	4683.67	76.71	1.00	1.00	0.96	1.04	0.84							
Inconsistent exposure periods	1012	1229.40	82.32	1.08	1.10	1.02	1.18	0.02							
Post-exposure periods	1330	1331.32	99.90	1.18	1.22	1.15	1.30	<0.001							

^a Rate is per 100 person years

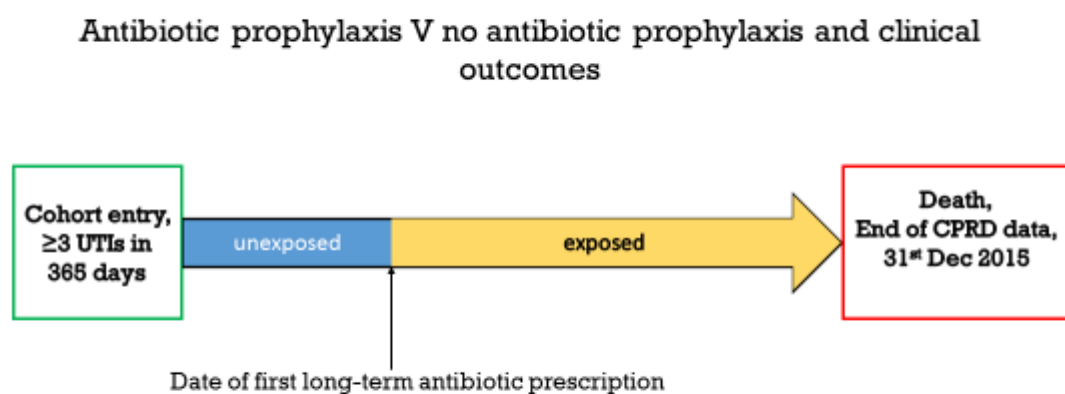
^b Lower confidence interval

^c Upper confidence interval

Supplementary Figure 1. Flow of patients from initial identification in the database through to final cohort.



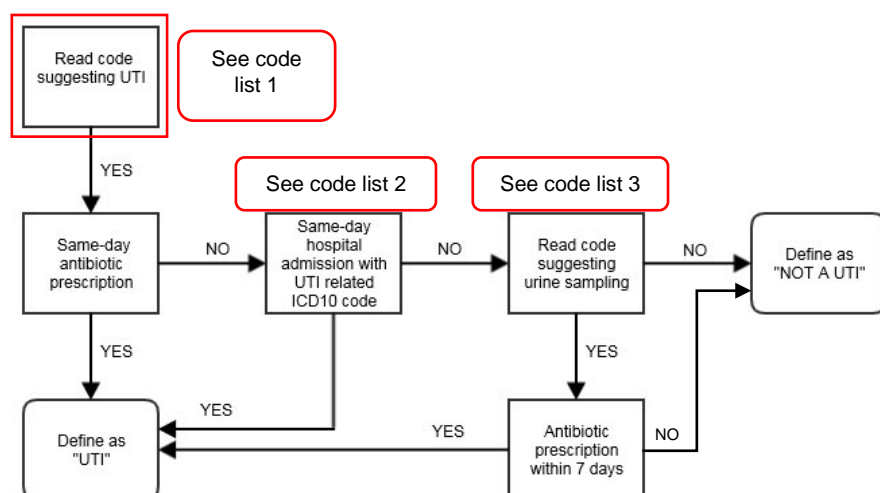
Supplementary Figure 2. Ascertainment of unexposed and exposed periods during patient follow-up.



Supplementary Appendix 1

Identifying UTI episodes using Read and ICD-10 codes

We identified UTI episodes using the following algorithm.



All cases were required to have at least one code indicating a diagnosis of UTI or a clinically relevant symptom.

Code List 1: Read codes suggesting UTI diagnosis or relevant symptom

Read code	readterm
K190300	Recurrent urinary tract infection
K190.11	Recurrent urinary tract infection
1AG..00	Recurrent urinary tract infections
K190z00	Urinary tract infection, site not specified NOS
K190500	Urinary tract infection
K190400	Chronic urinary tract infection
K190.00	Urinary tract infection, site not specified
K15..00	Cystitis
K150.00	Acute cystitis
14D4.00	H/O: recurrent cystitis
K155.00	Recurrent cystitis
K15z.00	Cystitis NOS
K152z00	Other chronic cystitis NOS
K152y00	Chronic cystitis unspecified
K15y.00	Other specified cystitis
K15yz00	Other cystitis NOS
1J4..00	suspected UTI
1A53.11	C/O - loin pain
R090C00	Loin pain
1A55.00	Dysuria
1A...12	Urinary symptoms
K197.00	Haematuria

1A1..11	Frequency of micturition
1979	Suprapubic pain
1A12.00	Frequency of micturition
1AZ6.00	Lower urinary tract symptoms

All cases then also needed at least one of the following:

- 1) A same-day antibiotic prescription**
- 2) A same-day hospital admission with a UTI relevant ICD-10 code (code list 2)**
- 3) A code indicating urine sent for culture (code list 3) and an antibiotic prescription within 7 days**

Code list 2: ICD-10 codes indicating a hospital diagnosis of UTI

N30.0	Acute cystitis
N30.9	Cystitis, unspecified
N39.0	Urinary tract infection, site not specified

Code list 3: Read code suggesting urine sent for culture

Read code	Read term
4JJ..12	Mid-stream urine sample
4JJ..12	Mid-stream urine sample
461..11	MSU - general
4JJ2.00	MSU sent for bacteriology
4JJ2.00	MSU sent for bacteriology
4JJ1.00	MSU sent for C/S
4JJ1.00	MSU sent for C/S
4615	MSU sent to lab.
4615	MSU sent to lab.
46U..00	Urine culture
46U..00	Urine culture
46U8.00	Urine culture - Bacteria OS
4JJ..13	Urine for culture
4JJ..13	Urine for culture
46f3.00	Urine leucocyte test = ++
46f4.00	Urine leucocyte test = +++
46D..00	Urine microscopy - general
	Urine microscopy - general
46DZ.00	NOS
46G..00	Urine microscopy: cells
46X0.00	Urine nitrite positive
4146	Urine sample sent to Lab
4JJ3.00	Urine sent for culture
4JJ3.00	Urine sent for culture

