Recurrent urinary tract infections and prophylactic antibiotic use in women: cross-sectional study.

Authors:

Dr Leigh Sanyaolu[1] - General Practitioner and Health and Care Research Wales, NIHR Doctoral Fellow. MRCGP, MRCS, PGDip, MBBCh(Hons), BSc(Hons).
Ms Victoria Best[2] - Research Officer and Data Scientist. MSc, BEng(Hons).
Dr Rebecca Cannings-John[3] - Principal Research Fellow in Statistics. PhD, MSc, BSc(Hons).
Professor Fiona Wood[1] – Professor of Medical Sociology. PhD, FHEA, MSc, BA(Hons).
Professor Adrian Edwards[1] - General Practitioner and Professor of General Practice, Division of Population Medicine. PhD, MRCP, MRCGP, MBBS, BMedSci.
Professor Ashley Akbari[2] – Professor of Population Data Science Research. MSc, BSc.
Associate Professor Gail Hayward[4] - General Practitioner, Associate Professor of Primary Care and Clinical Director of the NIHR Community Healthcare MedTech and IVD Cooperative. MBBChir, D.Phil, MRCP, DRCOG, MRCGP.
Dr Haroon Ahmed[1] - General Practitioner and Clinical Reader in Epidemiology. PhD, PGDip, MRCGP, MBBCh.

Affiliation: [1]Division of Population Medicine and PRIME Centre Wales, Cardiff University; [2]Population Data Science, Swansea University; [3]Centre for Trials Research, Cardiff University, [4]Nuffield Department of Primary Care Health Sciences, University of Oxford.

Corresponding author: Leigh Sanyaolu, **email**: SanyaoluLN@cardiff.ac.uk, **ORCID iD**: 0000-0002-6762-6986

How this fits in:

Little is known about the prevalence, characteristics, urine testing, or the use of prophylactic antibiotics amongst women with recurrent UTIs (rUTI). We found that 6.0% of women had evidence of rUTIs in Wales from 2010-2020, and of these 81% had a urine culture result in the preceding 12 months. 1.7% of women used prophylactic antibiotics during the study period, 64% had a urine culture result before starting prophylaxis, and of these 8% were resistant to the prescribed antibiotic. More frequent urine cultures in the workup of rUTI diagnosis and prophylactic antibiotic initiation could better inform antibiotic choice.

Key words: Urinary Tract Infection; Anti-Infective Agents, Urinary; Drug Resistance, Bacterial; Electronic Health Records; Cross-Sectional Studies

Abstract

Background: Despite the considerable morbidity caused by recurrent UTIs (rUTIs), and the wider personal and public health implications from frequent antibiotic use, few studies adequately describe the prevalence and characteristics of women with rUTIs or those who use prophylactic antibiotics.

Aim: To describe the prevalence, characteristics, and urine profiles of women with rUTIs with and without prophylactic antibiotic use in Welsh primary care.

Design and setting: Retrospective cross-sectional study in Welsh General Practice using the SAIL Databank.

Method: We describe the characteristics of women aged ≥18 years with rUTIs or using prophylactic antibiotics from 2010-2020, and associated urine culture results from 2015 – 2020.

Results: 6.0% of women (n=92,213) had rUTIs, and 1.7% (n=26,862) were prescribed prophylactic antibiotics. Only 49% of prophylactic antibiotic users met the definition of rUTIs before initiation. 81% of women with rUTIs had a urine culture result in the preceding 12 months with high rates of resistance to trimethoprim and amoxicillin. 64% of women taking prophylactic antibiotics had a urine culture result before initiation, and 18% (n=320) of women prescribed trimethoprim had resistance to it on the antecedent sample.

Conclusion: A substantial proportion of women had rUTIs or incident prophylactic antibiotic use. However, 64% of women had urine cultured before starting prophylaxis. There was a high proportion of cultured bacteria resistant to two antibiotics used for rUTI prevention and evidence of resistance to the prescribed antibiotic. More frequent urine cultures for rUTI diagnosis and before prophylactic antibiotic initiation could better inform antibiotic choices.

Keywords: Urinary Tract Infection; Anti-Infective Agents, Urinary; Drug Resistance, Bacterial; Electronic Health Records; Cross-Sectional Studies

Introduction

Urinary tract infections (UTIs) in women are common, and a proportion experience recurrent UTIs (rUTIs), defined as two or more UTIs in six months, or three or more in 12 months(1–3). Recurrent UTIs are a significant cause of morbidity and health service use(1,4,5). Estimates of the prevalence of rUTIs range from 3% to 44% of women, depending on the definition used and age or nationality studied(6–8). Women with rUTIs have frequent antibiotic exposure due to treatment for acute UTIs and potential long-term prophylaxis. Antibiotic exposure is a major driver of antimicrobial resistance (AMR), and antibiotic exposure for UTIs increases resistance within two months and persists for 12 months(9,10). Resistant UTIs have a greater impact on patients and are more costly to treat than susceptible infections(11,12).

Despite the considerable morbidity caused by rUTIs, and the wider personal and public health implications from frequent antibiotic use, few studies adequately describe the prevalence and characteristics of women with rUTIs. Furthermore, it is unclear how well clinical practice aligns with current guidelines recommending urine culture for rUTI diagnosis(1). Understanding real-world practice related to diagnosing and treating rUTIs, a common condition seen and managed in primary care, is an important step towards improving patient care.

This study aimed to comprehensively describe the prevalence, characteristics, urine testing, and susceptibility profiles of women with rUTIs in Wales to understand current clinical practice and alignment with guidelines.

Methods

Design

A cross-sectional study using anonymised individual-level, population-scale linked electronic health record (EHR) data sources within the Secure Anonymised Information Linkage (SAIL) Databank, the ISO27001 certified national trusted research environment (TRE) for Wales(13). All data sources within the SAIL Databank TRE are linkable following approvals using an anonymised linking field (ALF)(13). The data sources used include:

1. Welsh Longitudinal General Practice (**WLGP**) - primary care General Practice (GP) data using Read codes, covers 86% of the Welsh population registered with 82% of Welsh GPs (14,15),
2. Patient Episode Database for Wales (**PEDW**) – secondary care hospital admission data using the International Classification of Disease version 10 (ICD-10)(16),
3. Welsh Results Reporting Service (**WRRS**) - all Wales urine specimen data from primary and secondary care(17),
4. Welsh Demographic Service Dataset (**WDSD**) and Annual District Death Extract (**ADDE**) – demographic and death data(18,19).

Population

We created two cohorts. Cohort one included women who met the clinical definition of rUTIs (clinical cohort). Cohort two included women prescribed prophylactic antibiotics consistent with rUTI prevention (prophylaxis cohort; for definitions, see below). Eligibility criteria for the two cohorts are described in Table 1.

115 **Table 1.** Inclusion and exclusion criteria for study entry.

Inclusion criteria	1. Sufficient data linkage quality (see Supplementary Box 1). 2. Sex recorded as female using the WDSD(19). 3. Aged 18 years or over and alive during the study period (1st January 2010 to 31st December 2020). 4. Registered with a SAIL-providing GP during the study period. 5. Registered for at least 12 months before cohort entry for women with rUTIs or registered for at least 18 months before cohort entry for women taking prophylactic antibiotics (to capture co-morbidity and urine microbiology data). 6. Met the definition of a rUTI or prophylactic antibiotic use.
Exclusion criteria	1. Catheter use was recorded at any point before cohort entry. 2. Pregnancy was recorded in the 40 weeks before the cohort entry date to ensure women were not pregnant at cohort entry. Patients were eligible subsequently, provided they met the inclusion criteria and if pregnancy was not recorded within 40 weeks before the cohort entry date.

116

Table 2. Definitions of acute UTIs. 'Confirmed UTI' is defined as: bacterial growth of ≥ 10^8 CFU/L AND urine white cell count ≥ 10^8/L AND growth of an organism which is not candida. * Antibiotics were based on the National Institute for Health and Care Excellence UTI antimicrobial guidelines and included trimethoprim, nitrofurantoin, amoxicillin, pivmecillinam, cefalexin, fosfomycin, ciprofloxacin and co-amoxiclav(20–22).

	Clinical scenario	UTI-related Read code (WLGP data)	Antibiotic prescription* (WLGP data)	UTI-related ICD-10 code (PEDW data)	Urine culture result (WRRS data)	Time period between codes
1	GP clinically diagnosed & treated UTI	Yes	Yes	No	No	Same date.
2	Hospital diagnosed and treated UTI	No	No	Yes	No	Not applicable
3	GP clinically diagnosed, microbiologically confirmed and treated UTI	Yes	Yes	No	Confirmed UTI	Urine culture result within 7 days of GP clinically diagnosed and treated UTI. Earliest code = date of UTI.
4	Hospital diagnosed, microbiologically confirmed, and treated UTI	No	No	Yes	Confirmed UTI	Within 7 days. Earliest code = date of UTI.

Abbreviations: UTI – urinary tract infection, CFU/L – colony forming units per litre, ICD – International Classification of Diseases, GP - General Practitioner, PEDW - Patient Episode Database for Wales, WRRS – Welsh Results Reporting Service, WLGP - Welsh Longitudinal General Practice.

Case ascertainment

Definition of recurrent UTIs

We defined rUTIs as two or more acute UTIs within six months, or three or more within 12 months(1). We defined acute UTIs as shown in Table 2. Consultations and hospital admissions for acute UTIs were identified using Read and ICD-10 code lists (Supplementary Boxes 2-4). More than one acute UTI within a 28-day period was considered repeat consultations for the same episode. The date of the first consultation was recorded as the acute UTI date (Supplementary Figure 1). For hospital diagnosed UTIs, the start date of the UTI was the first date of an episode containing a UTI ICD-10 code, and the end date was its final date. The first time a woman met the definition of rUTI was used as the date of rUTI diagnosis.

Definition of prophylactic antibiotics

We defined prophylactic antibiotic use as at least three consecutive prescriptions for the same UTI-specific antibiotic (trimethoprim, nitrofurantoin or cefalexin) with 21 to 56 days between prescriptions (Supplementary Box 5 and Supplementary Figure 2). This approach was required as WLGP data includes prescribing data only (not dispensing) without data on the quantity of tablets prescribed. We excluded women who used prophylactic antibiotics in the preceding 12 months to identify new users and ascertain urine culture results before initiation.

Co-morbidity identification

We identified relevant co-morbidities that either increase the risk of UTIs or potentially influence antibiotic prescribing using Read codes and/or ICD-10 codes in the WLGP and PEDW data sources respectively. To define these, we looked back from the date of cohort entry. The length of lookback was specific to the condition, and further details are included in Supplementary Box 6.

Urine microbiology

Reported urine culture results were identified using code lists for urine tests in the WRRS (Supplementary Box 7). We restricted analyses of urine specimens to 2015-2020 since there was a marked increase in NHS Wales laboratories submitting urine data from 2015(23). Urine culture results reported on the same day with the same result were regarded as duplicates. We categorised urine microbiology results using a methodology based on the Public Health Wales Microbiology Division's standard operating procedure using organism(s) cultured and white blood cell count (Supplementary Box 8)(24). We categorised antibiotic susceptibility using the European Committee on Antimicrobial Susceptibility Testing guidelines 2019, where intermediate is described as susceptible at increased exposure(25).

We analysed all reported urine culture results in the 12 months before diagnosis (clinical cohort) and 18 months before prophylactic antibiotic initiation (prophylactic cohort) and all urine culture results within seven days of an acute UTI to define the number of women with microbiologically confirmed rUTIs. The rationale for using 18 months prior to study entry for the prophylactic cohort was to account for potential delays between rUTI diagnosis and investigation or referral before initiating antibiotics.

Statistical analysis

We summarised sociodemographic and clinical characteristics using counts and percentages for categorical variables and means (with standard deviation (SD)) or medians (with interquartile range (IQR)) for continuous variables. We calculated rates according to 10-year age bands using all women in SAIL aged 18 years and over and their person-time over the study period (2010-2020) as the denominator.

For women in both cohorts, we reported the number of urine cultures before cohort entry, organisms cultured, and antibiotic susceptibility with sub-group analyses for *E. Coli* and coliforms. We also explored whether the proportions of urine cultures tested for susceptibility and the proportion that were resistant changed over the study period in view of changing incident prophylactic antibiotic use in the prophylaxis cohort. For women in the prophylaxis cohort, we also reported antibiotic type and dose and calculated how many met the definition of rUTIs. For those who did, we calculated time between meeting the rUTI definition and starting prophylactic antibiotics. We conducted sensitivity analyses restricting prophylactic antibiotic use to women on a consistent dose of antibiotics over consecutive prescriptions and adjusted our definition of acute UTIs to describe the proportion of women with rUTIs before starting prophylaxis to assess their impact on our estimates. Finally, we estimated how many women had a urine culture reported before initiating prophylactic antibiotics and used the most recent result before initiation, to ascertain their prophylactic antibiotic susceptibility.

Analyses were conducted in R version 4.1.3(26). The SAIL Databank Information Governance Review Panel (IGRP) approved the study. For analyses where counts are small, counts are rounded to the nearest 10 for the purposes of disclosure control and privacy protection. We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist to guide reporting(27).

Results

We identified 92,213 women (6.0% of women aged 18 years or over between 2010-2020) who met the clinical definition of rUTIs and were entered into the clinical cohort (Figure 1). Median age was 60 years (IQR 38.0–76.0). The rate of women with rUTIs followed a 'J' shaped pattern rising with increasing age (Figure 2). We identified 26,862 women (1.7%) with prescriptions for prophylactic antibiotics who formed the prophylaxis cohort (Figure 1). Median age was 71 years (IQR 55.1-81.6). In all, 17,803 were present in both cohorts.

Prophylactic antibiotic initiation increased initially until 2012 before declining from 2013 (Supplementary Figure 3). Trimethoprim and cefalexin use declined with time, and nitrofurantoin use increased. The most used prophylactic antibiotic was trimethoprim (Supplementary Figure 4). A small proportion (<1%) of women appeared to be using multiple antibiotics concurrently. Most women were taking a consistent dose of the prophylactic antibiotic across the consecutive prescriptions (n=20,892, 78%). The most prescribed dosages for trimethoprim were 100mg and 200mg, for nitrofurantoin were 50mg or 100mg, and for cefalexin were 250mg and 500mg.

The two cohorts were similar in terms of ethnic group and deprivation (Table 3). Most women with rUTIs were fit or had mild frailty according to the electronic frailty index (eFI), whereas for prophylactic antibiotic users all levels of frailty were higher (Table 3)(28,29).

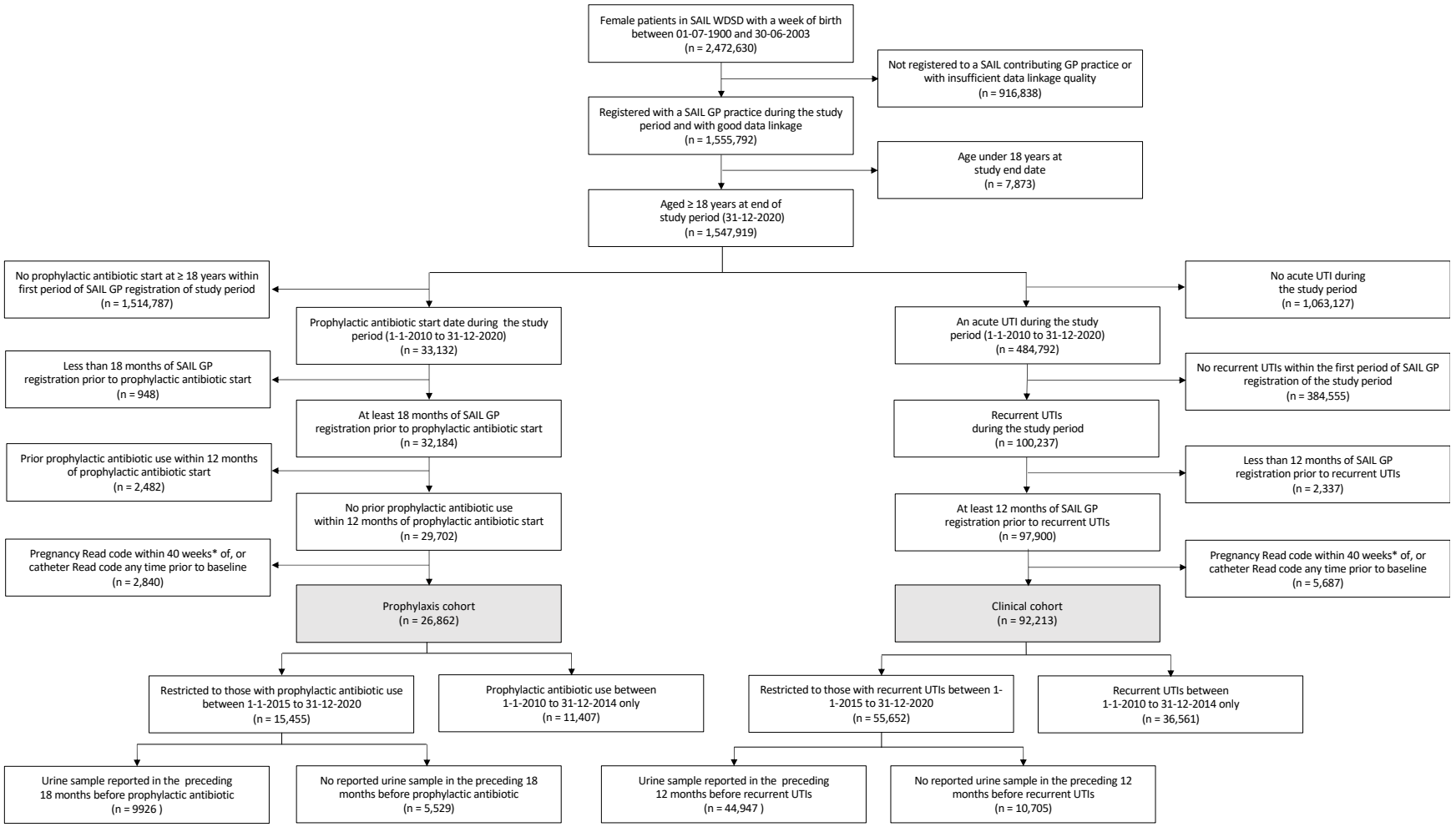

Figure 1. CONSORT flow charts for final study cohorts. *Pregnancy Read codes recorded against individuals aged 55 and over at time of pregnancy event are assumed to be a coding error and are therefore retained within the project cohort. Abbreviations: WDSD = Welsh Demographic Service Datase

Table 3. Sociodemographic and clinical characteristics of women with recurrent UTIs and prophylactic antibiotic users.

Cohort characteristic	Level	Women with recurrent UTIs (clinical cohort)	Prophylactic antibiotic users (prophylaxis cohort)
Total cohort population n		92,213	26,862
Age in years (median [IQR])		60.0 [38.0, 76.0]	70.6 [55.1, 81.6]
Ethnic group (%)	White	51,446 (55.8)	15,526 (57.8)
	All other ethnic groups combined	1,368 (1.5)	241 (0.9)
	Missing	39,399 (42.7)	11,095 (41.3)
Deprivation quintile, WIMD n (%)	1 (most deprived)	18,069 (19.6)	5,064 (18.9)
	2	17,790 (19.3)	5,386 (20.1)
	3	17,751 (19.2)	5,133 (19.1)
	4	16,896 (18.3)	4,893 (18.2)
	5 (least deprived)	18,339 (19.9)	5,352 (19.9)
	Missing	3,368 (3.7)	1,034 (3.8)
BMI (median [IQR]) *		26.0 [23.0, 31.0]	27.0 [23.0, 31.0]
Smoking status n (%)	Never smoked	37,786 (41.0)	10,905 (40.6)
	Ex-smoker	34,042 (36.9)	10,992 (40.9)
	Current smoker	14,882 (16.1)	3,423 (12.7)
	Missing	5,503 (6.0)	1,542 (5.7)
Alcohol status n (%)	Non-drinker	32,996 (35.8)	11,485 (42.8)
	Current drinker	43,611 (47.3)	12,118 (45.1)
	Excess drinker	2,419 (2.6)	604 (2.2)
	Missing	13,187 (14.3)	2,655 (9.9)
Diagnosis location of UTIs contributing to recurrent UTI diagnosis n (%)	General Practice	76,233 (82.7)	N/A
	Hospital	5,490 (6.0)	N/A
	Both	10,490 (11.4)	N/A
Frailty score via eFI n (%)	Fit	40,300 (43.7)	7,070 (26.3)
	Mild frailty	30,793 (33.4)	10,372 (38.6)
	Moderate frailty	14,742 (16.0)	6,495 (24.2)
	Severe frailty	6,378 (6.9)	2,925 (10.9)
Diabetes n (%)		20,410 (22.1)	7,676 (28.6)
Chronic kidney disease stage 3-5 n (%)		12,827 (13.9)	5,348 (19.9)
Immunosuppression n (%)		4,991 (5.4)	2,060 (7.7)
Renal stones n (%)		412 (0.4)	258 (1.0)
Urinary tract structural abnormality n (%)		1,249 (1.4)	565 (2.1)

***** BMI was missing for 21,415 patients in the clinical cohort and 5,411 patients in the prophylaxis cohort. **Abbreviations:** WIMD = Welsh Index of Multiple Deprivation, BMI = body mass index, eFI = electronic frailty index, N/A = not applicable.

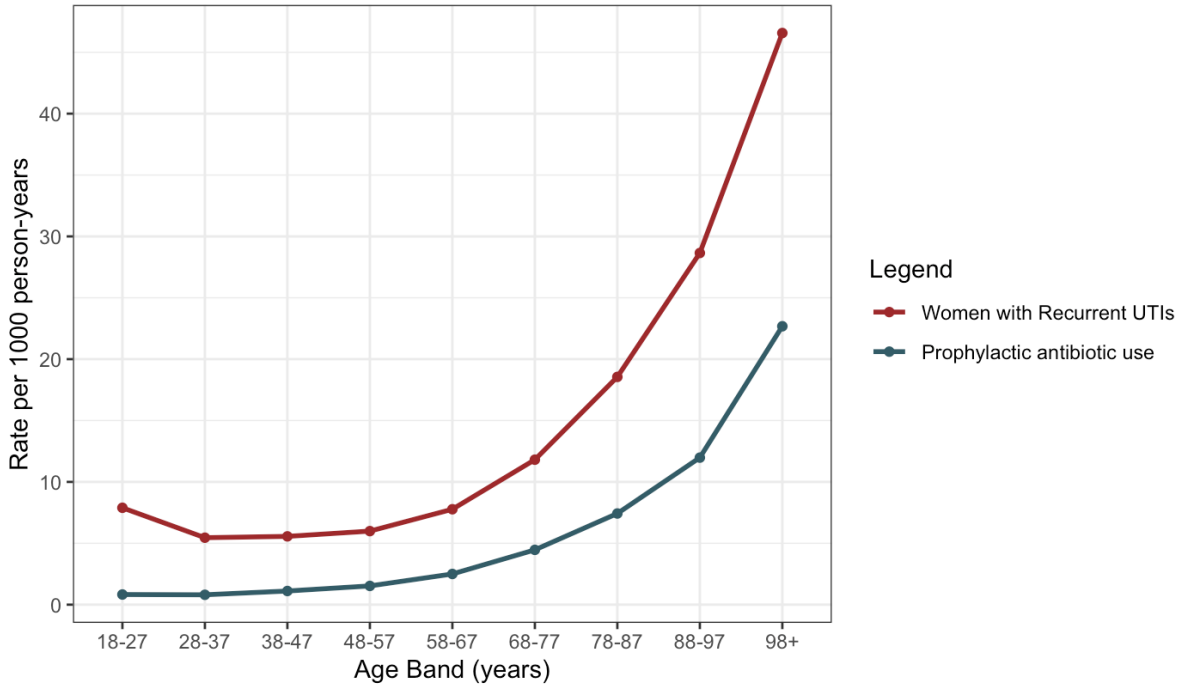

Figure 2. The rate of women with rUTIs and prophylactic antibiotic use over the study period according to age band.

Clinical cohort

When the clinical cohort was restricted to those with rUTIs between 2015 to 2020, the cohort reduced to 55,652 women and 125,971 urine culture results. Of these, 44,947 (80.8%) women had a urine culture reported in the preceding 12 months. Over 40% (n=18,475) had three or more samples reported. Of all urine cultures reported, 28.1% (n=35,404) showed microbiological evidence of a UTI (Supplementary Figure 5) with *E. Coli* the most cultured uropathogen (n=41,987, 76.8%) (Supplementary Figure 6). Based on urine culture results within seven days of an acute UTI, 5.1% (n=2,866) had microbiologically confirmed rUTIs (i.e. all UTIs contributing to the rUTI diagnosis were microbiologically confirmed). Antibiotic susceptibility testing was low (under 40%) for most antibiotics except, trimethoprim, nitrofurantoin and amoxicillin. Trimethoprim and amoxicillin had high rates of resistance (Table 4).

Prophylaxis cohort

In the prophylaxis cohort, 49% (n=13,149) of women met the definition of rUTIs in the preceding 18 months. Of these, 39% (n=5,139) started prophylactic antibiotics within 3 months of meeting the rUTI definition (Supplementary Figure 7).

When restricted to incident prophylactic antibiotic users between 2015-2020, the cohort reduced to 15,455 women and 53,988 urine culture results. Of these, 64% (n=9,926) had at least one urine culture reported in the preceding 18 months and of these 77% (n=7,641) had three or more samples reported. Of reported urine cultures, 32% (n=17,367) were microbiologically confirmed UTIs, *E.coli* was the predominant organism (76%, n=19,669) cultured and 42.8% (n=6,611) had at least one microbiologically confirmed UTI before starting

prophylactic antibiotics (Supplementary Figures 8-9). Of women taking prophylactic antibiotics between 2015-2020, 49.8% (n=7,695) had clinical rUTIs before initiation and of these 6.1% (n=472) had microbiologically confirmed rUTIs. Like the clinical cohort, antibiotic susceptibility for trimethoprim and amoxicillin showed high rates of resistance (Table 4). However, the proportions of urine cultures growing any organism with evidence of resistance to trimethoprim or amoxicillin decreased over the study period (Supplementary Figure 10).

Based on the most recent urine culture result that cultured an organism (n=4983), 8% (n=410) of prophylactic antibiotic users had evidence of resistance to that antibiotic (Supplementary Table 1). This was highest in those taking trimethoprim (n=320, 18%), with a downward trend over the study period (Supplementary Figure 11). Resistance was lower for those taking nitrofurantoin (which was consistent over the study period) and cefalexin (trend not shown due to small numbers) (Supplementary Figure 11 and Supplementary Table 1). Resistance to these three prophylactic antibiotics, irrespective of which antibiotic was prescribed, was 42% for trimethoprim, 6% for nitrofurantoin and 3% for cefalexin.

Table 4. Antibiotic susceptibility for all urine culture results that cultured any organism, *E. Coli* and coliforms. The resistance levels for cefalexin should be interpreted with caution since the proportions of urine cultures tested for susceptibility to cefalexin was low suggesting selective testing.

		Susceptibility for urine culture results culturing any organism (Clinical cohort N=54,667, prophylaxis cohort N=25,984)		**Susceptibility for urine culture results culturing *E. Coli* (Clinical cohort N=41,987, prophylaxis cohort N=19,669)**		**Susceptibility for urine culture results culturing a coliform (Clinical cohort N=50,119, prophylaxis cohort N=23,784)**	
		Proportion tested (%)	**Resistance (%)**	**Proportion tested (%)**	**Resistance (%)**	**Proportion tested (%)**	**Resistance (%)**
Clinical cohort	Trimethoprim	94.9	40.3	98.3	41.4	98.1	40.6
	Nitrofurantoin	93.8	8.2	97.4	2.9	95.7	8.6
	Amoxicillin	82.1	57.1	82.8	56.8	83.4	60.5
	Cefalexin	23.6	15.8	23.6	14.6	24.9	15.0
Prophylaxis cohort	Trimethoprim	95.3	44.6	98.7	46.5	98.6	44.9
	Nitrofurantoin	95.0	8.8	98.2	3.2	96.9	9.2
	Amoxicillin	85.2	59.6	85.9	60.0	86.6	63.4
	Cefalexin	27.1	14.5	27.4	13.4	28.7	13.6

Sensitivity analyses only defining prophylactic antibiotic use if the dose prescribed was consistent across consecutive prescriptions did not meaningfully affect our estimates (Supplementary Table 2). Changing the minimum time between acute UTIs and changing our definition of an acute UTI to include Read codes only did not meaningfully impact our estimate of women with rUTIs prior to starting prophylaxis (Supplementary Table 3). Changing our acute UTI definition to include only UTI-related antibiotics did increase the proportion of women with rUTIs before starting prophylaxis to 74% (n=19,970).

Discussion

Summary

This is the first population-based study to describe the prevalence of rUTIs, prophylactic antibiotic use, and associated microbiology in women in the UK. We found that of women registered with a SAIL data providing GP in Wales between 2010-2020, 6.0% had rUTIs, and 1.7% was prescribed prophylactic antibiotics with the proportions rising sharply around 58-67 years. Nearly half of prophylactic antibiotic users met the rUTI definition in the 18 months before initiation, and initiation of prophylactic antibiotics decreased over the study period.

Over 80% of women with rUTIs had a urine culture reported in the 12 months before the diagnosis with high levels of resistance to trimethoprim and amoxicillin. Microbiological evidence of a UTI was present in 28% of all reported urine cultures. Urine culture before initiating prophylactic antibiotics was reported in over 60%. Nearly 20% of women prescribed trimethoprim prophylactically had evidence of resistance to it before initiation.

Strengths and limitations

We used a large population-based sample to identify women with rUTIs and prescribed prophylactic antibiotics with linked urine microbiology including all urine culture within NHS Wales. We comprehensively reported urine microbiology results and resistance patterns. Our study population was representative of women in the wider Welsh population and women with and without adequate lookback data had similar characteristics(14) (Supplementary Figures 12-17). A conservative estimate of rUTI prevalence is likely both from using a 28-day window to avoid capturing UTI-relapse and not having data from out-of-hours GP or hospital attendances not requiring admission. We used UTI-related codes to identify acute UTIs but if clinicians had used non-specific codes these UTIs would not be captured, again under-estimating rUTI prevalence. Due to these potential limitations, when describing the proportion of women with rUTIs before prophylactic antibiotic initiation, we adjusted both the minimum time between UTIs and our definition of an acute UTI to include only UTI-specific Read codes (and potentially capture UTIs diagnosed in out-of-hours GP or hospital attendances) or to include only antibiotics in sensitivity analyses. Changing the time between UTIs and defining an acute UTI based on UTI-specific Read codes had minimal impact (Supplementary table 3). Changing the definition of an acute UTI to include only antibiotics, increased the proportion with rUTIs but likely overestimated the true value (Supplementary Table 3). Finally, the data we used are primarily used for clinical practice, not research, with risks of coding errors, missing data and misclassification. Misclassification of prophylactic antibiotics is possible where women we defined as prophylactic antibiotic users could have had three acute antibiotic courses. We used a variety of methods to reduce this risk such as using a fixed timeframe between prescriptions and conducting a sensitivity analysis to assess

the robustness of our estimates. Finally, the diagnosis of UTIs is especially challenging in older, frailer women where symptoms can be less specific, and they may have asymptomatic bacteriuria and thus be misdiagnosed as having a UTI. This could potentially falsely elevate the prevalence of rUTIs, however we used UTI specific Read codes in addition to antibiotic prescriptions to try to mitigate for this.

Comparison with existing literature

To our knowledge there is only one other study using population-based data describing women with rUTIs(30). This US-based study identified women with incident rUTIs and found 61% of women had at least one urine culture over 12 months before diagnosis, lower than the proportion we found. Our study cohort likely includes both incident and prevalent rUTIs as we did not stipulate a UTI-free period prior to rUTI cohort entry. Therefore urine culture, as per guidelines, might be more likely occur in our cohort in those with prevalent rUTIs. The US-based study also found a 'J' shaped curve for the incidence rate of rUTIs according to age. This likely relates to UTI risk factors such as sexual intercourse in early adulthood (5,31) and hormonal changes of the menopause accounting for the increased rate at about 55 years (typical age of menopause is between 45 and 55 years(31–35)). In terms of rUTI prevalence, our results suggest the prevalence is higher than that of a survey conducted in 2015 which found a prevalence of 3%(8). This is not surprising as certain populations such as frail women or those with cognitive impairment may not complete a survey, whereas they are more likely included in our cohort.

Prophylactic antibiotic use in our study declined from 2013 to 2020. Overall antibiotic prescribing followed a similar pattern in both Wales and England aligning with UK Government's strategy to reduce antibiotic use and combat increasing AMR (36–38). Resistance in UTIs is an increasing problem and evidence of UTI resistance patterns in women with rUTIs is limited. Our study shows that trimethoprim and nitrofurantoin resistance in women with rUTI are comparable to those reported in a 2018 and 2023 Public Health Wales (PHW) report(39,40). This suggests resistance in women with rUTIs is not significantly higher than resistance patterns overall.

Implications for practice

It could be clinically beneficial to encourage microbiological confirmation of rUTIs in primary care and before prophylactic antibiotic initiation in line with clinical guidelines (5,31). Women with rUTIs in our study had high levels of resistance to trimethoprim and amoxicillin which are two of the four prophylactic antibiotics recommended in the UK(31). A low proportion of urine cultures reported susceptibility to cefalexin, and although resistance levels were relatively low they should be interpreted with caution due to likely selective testing. Despite low resistance levels, nitrofurantoin has limitations in chronic kidney disease and can result in lung and liver fibrosis with the risk increasing with age and duration of use(41–43). Our study has also shown that nearly 20% of women prescribed trimethoprim had evidence of resistance before initiation. These findings emphasise urine culture's potential importance in informing prophylactic antibiotic choice. However, increasing urine culture has limitations due to negative culture results, culturing a mixed growth of organisms or the initiator, in primary or secondary care, not having access to all recent urine microbiology results.

Conclusion

This is the first population-based study on rUTIs and prophylactic antibiotic use in women including urine microbiology. The prevalence of rUTIs in women and the incident use of prophylactic antibiotics, although declining with time, in Wales was substantial especially in older women. Women with rUTIs had high levels of resistance to two of the four recommended prophylactic antibiotics, 64% had urine culture before starting prophylactic antibiotics and a significant proportion had evidence of resistance to that antibiotic. As part of rUTI diagnosis and before initiating prophylactic antibiotics, more frequent urine cultures could better inform antibiotic choice for prophylaxis and treatment.

Acknowledgements: This study makes use of anonymised data held in the Secure Anonymised Information Linkage (SAIL) Databank. We would like to acknowledge all the data providers who make anonymised data available for research.

Funding: This work was supported by the Welsh Government through Health and Care Research Wales (NIHR-FS-2021-LS to L.N.S).

Patient and public involvement (PPI): The Improving Prophylactic Antibiotic use for Recurrent urinary Tract infection (IMPART) PPI team were involved in the design of this study.

Transparency declaration: None to declare.

Ethical approval and Data availability statement: The data used in this study are available in the SAIL Databank at Swansea University, Swansea, UK, but as restrictions apply, they are not publicly available. All proposals to use SAIL data are subject to review by an independent Information Governance Review Panel (IGRP). Before any data can be accessed, approval must be given by the IGRP. The IGRP carefully considers each project to ensure the proper and appropriate use of SAIL data. When access has been granted, it is gained through a privacy-protecting trusted research environment (TRE) and remote access system referred to as the SAIL Gateway. SAIL has established an application process to be followed by anyone who would like to access data via SAIL at https://www.saildatabank.com/application-process. The SAIL Databank IGRP approved the study, project approval number 1169.

The code for preparing the data in SAIL and the analytical R code are available on reasonable request to the lead author.

References

1. Bonkat G, Bartoletti R, Bruyère T et al. EAU Guidelines on Urological infections [Internet]. 2023 [cited 2023 Jun 22]. Available from: https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Urological-infections-2023.pdf
2. Foxman B. Epidemiology of urinary tract infections: Incidence, morbidity, and economic costs. Am J Med. 2002;113(1A):5S-13S.
3. Dason S, Dason JT, Kapoor A. Guidelines for the diagnosis and management of recurrent urinary tract infection in women. Can Urol Assoc J. 2011;5(5):316–22.
4. Sanyaolu LN, Hayes C V., Lecky DM et al. Patients' and Healthcare Professionals' Experiences and Views of Recurrent Urinary Tract Infections in Women: Qualitative Evidence Synthesis and Meta-Ethnography. Antibiotics. 2023;12(3):434.
5. National Institute for Health and Clinical Excellence (NICE). Urinary tract infection (recurrent): antimicrobial prescribing. National Institute for Health and Care Excellence. [Internet]. 2018 [cited 2020 Jul 23]. Available from: https://www.nice.org.uk/guidance/ng112/evidence/evidence-review-pdf-6545656621
6. Ikahelmo R, Siitonen A, Heiskanen T et al. Recurrence of Urinary Tract Infection in a Primary Care Setting: Analysis of a I-Year Follow-up of 179 Women. Clin Infect Dis. 1996;22(1):91–9.
7. Foxman B, Gillespie B, Koopman J et al. Risk Factors for Second Urinary Tract Infection among College Women. Am J Epidemiol. 2000;151(12):1194-205.
8. Butler CC, Hawking MKD, Quigley A, McNulty CAM. Incidence, severity, help seeking, and management of uncomplicated urinary tract infection: A population-based survey. Br J Gen Pract. 2015;65(639):e702–7.
9. Costelloe C, Metcalfe C, Lovering A et al. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: Systematic review and meta-analysis. BMJ. 2010;340(7756):1120.
10. Chatterjee A, Modarai M, Naylor NR et al. Quantifying drivers of antibiotic resistance in humans: a systematic review. Lancet Infect Dis. 2018;18(12):e368–78.
11. Butler CC, Hillier S, Roberts Z et al. Antibiotic-resistant infections in primary care are symptomatic for longer and increase workload: Outcomes for patients with E. coli UTIs. Br J Gen Pract. 2006;56(530):686–92.
12. Alam MF, Cohen D, Butler C et al. The additional costs of antibiotics and re-consultations for antibiotic-resistant Escherichia coli urinary tract infections managed in general practice. Int J Antimicrob Agents. 2009;33(3):255–7.
13. Lyons RA, Jones KH, John G et al. The SAIL databank: Linking multiple health and social care datasets. BMC Med Inform Decis Mak. 2009;9(1):1–8.
14. Jones C. WLGP coverage report [Internet]. 2023 [cited 2023 Sep 5]. Available from: https://docs.hiru.swan.ac.uk/display/SATP/WLGP+coverage+reports?preview=/142149774/240058557/GP%20Data%20-%20RMarkdown%20Full%20Report%20-%202022-04-01%20-%202023-03-31.pdf

15. SAIL Databank. Welsh Longitudinal General Practice Dataset (WLGP) - Welsh Primary Care [Internet]. [cited 2023 Jun 22]. Available from: https://web.www.healthdatagateway.org/dataset/33fc3ffd-aa4c-4a16-a32f-0c900aaea3d2
16. SAIL Databank. Patient Episode Dataset for Wales (PEDW) [Internet]. [cited 2023 Jun 22]. Available from: https://web.www.healthdatagateway.org/dataset/4c33a5d2-164c-41d7-9797-dc2b008cc852
17. SAIL Databank. Welsh Results Reports Service (WRRS) [Internet]. [cited 2023 Jun 22]. Available from: https://web.www.healthdatagateway.org/dataset/71d37610-ac55-432d-82a3-bdb04407acd8
18. SAIL Databank. Annual District Death Extract (ADDE) [Internet]. [cited 2023 Oct 11]. Available from: https://web.www.healthdatagateway.org/dataset/15cf4241-abad-4dcc-95b0-8cd7c02be999
19. SAIL Databank. Welsh Demographic Service Dataset (WDSD) [Internet]. [cited 2023 Sep 5]. Available from: https://web.www.healthdatagateway.org/dataset/8a8a5e90-b0c6-4839-bcd2-c69e6e8dca6d
20. National Institute for Health and Care Excellence. Urinary tract infection (recurrent): antimicrobial prescribing. 2018. Available from: https://www.nice.org.uk/guidance/ng112/resources/urinary-tract-infection-recurrent-antimicrobial-prescribing-pdf-66141595059397
21. National Institute for Health and Care Excellence (NICE). NICE Guideline. 2018. Urinary tract infection (lower): antimicrobial prescribing. Available from: www.nice.org.uk/guidance/ng109
22. National Institute for Health and Care Excellence (NICE). NICE guideline. 2018. Pyelonephritis (acute): antimicrobial prescribing. Available from: www.nice.org.uk/guidance/ng111
23. Davies G, Akbari A, Abbasizanjani H et al. The Welsh Results Reports Service (WRRS) Data: Wales Population-Scale Pathology Data, A National Data Asset [Internet]. [cited 2023 Jun 22]. Available from: https://saildatabank.com/wp-content/uploads/2022/04/Data-Explained-The-Welsh-Results-Reports-Service-WRRS-Data.pdf
24. Microbiology Division Public Health Wales. CDBBA 041. Bench Aid: Investigation of Urine. 2021.
25. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 13.0, 2023. http://www.eucast.org.
26. R Core Team (2023). _R: A Language and Environment for Statistical Computing_. R Foundation for Statistical Computing, Vienna, Austria. <https://www.R-project.org/>.
27. von Elm E, Altman DG, Egger M et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008 Apr;61(4):344–9.

28. Clegg A, Bates C, Young J et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age Ageing. 2016 May 1;45(3):353–60.
29. Hollinghurst J, Fry R, Akbari A et al. External validation of the electronic Frailty Index using the population of Wales within the Secure Anonymised Information Linkage Databank. Age Ageing. 2019 Nov 1;48(6):922–6.
30. Suskind AM, Saigal CS, Hanley JM et al. Incidence and Management of Uncomplicated Recurrent Urinary Tract Infections in a National Sample of Women in the United States. Urology. 2016 Apr 1;90:50–5.
31. National Institute for Health and Care Excellence (NICE). Urinary tract infection (lower) - women: Scenario: Suspected recurrent UTI without haematuria in women who are not catheterized or pregnant. [Internet]. 2023 [cited 2023 Jun 25]. Available from: https://cks.nice.org.uk/topics/urinary-tract-infection-lower-women/management/recurrent-uti-no-visible-haematuria-not-pregnant-or-catheterized/
32. Arnold JJ, Hehn LE, Klein DA. Common Questions About Recurrent Urinary Tract Infections in Women. Am Fam Physician. 2016 Apr 1;93(7):560-9
33. Raz R, Gennesin Y, Wasser J et al. Recurrent Urinary Tract Infections in Postmenopausal Women. Clin Infect Dis. 2000 Jan;30(1):152-6.
34. Perrotta C, Aznar M, Mejia R et al. Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. Cochrane Database of Systematic Reviews. 2008;(2):CD005131(2).
35. National Institute for Health and Care Excellence (NICE). Menopause: diagnosis and management - NICE guideline [NG23] [Internet]. 2015 [cited 2022 Oct 6]. Available from: https://www.nice.org.uk/guidance/ng23/ifp/chapter/menopause
36. Thomson K, Berry R, Robinson T et al. An examination of trends in antibiotic prescribing in primary care and the association with area-level deprivation in England. BMC Public Health. 2020 Aug 3;20(1).
37. Adekanmbi V, Jones H, Farewell D, Francis NA. Antibiotic use and deprivation: An analysis of Welsh primary care antibiotic prescribing data by socioeconomic status. J Antimicrob Chemother. 2020;75(8):2363–71.
38. Department of Health, Department for Environment Food and Rural Affairs. UK Five Year Antimicrobial Resistance Strategy 2013 to 2018. Department of Health Department for Environment Food and Rural Affairs [Internet]. 2013;43. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf
39. Heginbothom M, Howe R, Davies E. A Report from Public Health Wales Healthcare Associated Infection, Antimicrobial Resistance & Prescribing Programme (HARP team): Antimicrobial Resistance in Wales 2008-2017. [Internet]. 2018 [cited 2023 Feb 4]. Available from: https://phw.nhs.wales
40. Heginbothom M, Boots S, Sutton D, Davies M, Howe R. Public Health Wales NHS Trust: Antibacterial Resistance in Blood Cultures in Wales 2016- 2022 [Internet]. 2023. Available from: https://phw.nhs.wales/

41. Claussen K, Stocks E, Bhat D et al. How Common Are Pulmonary and Hepatic Adverse Effects in Older Adults Prescribed Nitrofurantoin? J Am Geriatr Soc . 2017;65(6):1316–20.
42. Muller AE, Verhaegh EM, Harbarth S et al. Nitrofurantoin's efficacy and safety as prophylaxis for urinary tract infections: a systematic review of the literature and meta-analysis of controlled trials. Clin Microbiol Infect. 2017 Jun;23(6):355-362.
43. Medicines and Healthcare products Regulatory Agency. Nitrofurantoin: reminder of the risks of pulmonary and hepatic adverse drug reactions. Drug Safety Update volume 16, issue 9: April 2023: 3.