Prophylactic antibiotics to prevent recurrent urinary tract infections and risk of antibiotic resistance: target trial emulation with the SAIL Databank

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Summary

Background Prophylactic antibiotics are recommended for the prevention of recurrent urinary tract infections (rUTIs) but can cause antibiotic resistance, a growing global concern. Estimates of the absolute risk of resistance with prophylactic antibiotic use are limited. We aimed to estimate the effect of prophylactic antibiotic use on antibiotic resistance in women with rUTIs.

Methods We did a retrospective cohort study within the target trial framework using electronic health records of Welsh residents held by the Secure Anonymised Information Linkage (known as SAIL) Databank. We emulated a pragmatic trial of women aged 18 years or older with rUTIs, comparing the initiation of prophylactic antibiotics versus non-initiation. The primary outcome was hospital admission with an antibiotic-resistant infection by 52 weeks. Secondary outcomes were hospital admission with an antibiotic-resistant urine infection and uropathogen antibiotic resistance to one or more or two or more antibiotics. Using the survival probabilities, we calculated the risk, risk ratio, risk difference, and number needed to harm of each outcome for each treatment strategy by 52 weeks.

Findings We identified 48 297 women in the SAIL Databank who were eligible for inclusion between Jan 1, 2015, and Dec 31, 2020, of whom 839 initiated prophylactic antibiotics. 616 women were admitted to hospital with an antibiotic-resistant infection by 52 weeks (thus, meeting the primary outcome). Prophylactic antibiotics did not increase the risk of hospital admission with an antibiotic-resistant infection by 52 weeks, with a risk of 1·4% (95% CI 1·3–1·5) in the non-antibiotic group and a risk of 1·9% (1·0–3·1) in the antibiotic prophylaxis group (risk ratio 1·41; 95% CI 0·74–2·24). Furthermore, the risk of admission with an antibiotic-resistant urine infection did not increase with prophylactic antibiotics (1·56, 0·76–2·49). However, prophylactic antibiotics increased the risk of uropathogen resistance to at least one antibiotic on urine culture (risk ratio 1·29, 95% CI 1·14–1·44) and resistance to two or more antibiotics on urine culture (1·57, 1·37–1·79).

Interpretation In our target trial emulation, prophylactic antibiotic use did not increase the risk of hospital admission with an antibiotic-resistant infection or urine infection, but it did increase the risk of uropathogen antibiotic resistance and multidrug antibiotic resistance on urine culture. This study provides new data for the absolute risk and number needed to harm for individual-level antibiotic resistance that could be used to support shared decision-making discussions on rUTI prevention.

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Introduction

Antibiotic resistance is a global and public health emergency. In 2019, antibiotic-resistant infections were directly responsible for 1·27 million deaths globally.[1] Without action, this figure is expected to rise to 1·91 million deaths by 2050.[2] Antibiotic use is a major driver of antibiotic resistance, and antibiotic stewardship is vital to slow future resistance rates.[3] Recurrent urinary tract infections (rUTIs), defined as two or more urinary tract infections (UTIs) in 6 months or three or more in 12 months, have an estimated prevalence of 6% in women in the UK and can lead to substantial antibiotic use.[4,5] rUTIs have a considerable impact on quality of life, and some women and health-care professionals are concerned about the development of resistant infections.[6]

Current guidelines recommend daily low-dose prophylactic antibiotics for rUTI prevention when behavioural and non-antibiotic prophylaxis have been proven ineffective.[7] However, the benefits of prophylactic antibiotics need to be balanced against the harms of antibiotic resistance.[7,8] Few studies have assessed the impact of long-term prophylactic antibiotic use on antibiotic resistance.[9] This information is vital for shared decision making between patients and health-care professionals about rUTI prevention.

Estimating the risk of antibiotic resistance from prophylactic antibiotic use would ideally be addressed

See Online for appendix

Research in context

Evidence before this study

We searched MEDLINE (Ovid) for published articles, without language restrictions, from database inception until Jan 23, 2023, and updated the search on Jan 16, 2026. The search strategy included a methodological filter (appendix p 12) for women as follows. We used MeSH terms and journal names related to sex and gender, including "Gender Identity", "Sex Characteristics", "Sex Determination", "Sex Distribution", "Sex Factors", "Women" (exploded), "Women's Health", "Women's Health Services", and journals such as *Health Care for Women International*, *Journal of the American Medical Women's Association*, *Women & Health*, and *Women's Health Issues*. We also included these free-text terms in titles and abstracts: "female*", "gender*", "girl*", "mother*", "widow*", "woman*", and "women*". We did a conceptual search for recurrent urinary tract infections (rUTIs). We used three conceptual blocks, each within three words of the others in titles and abstracts. Recurrence-related terms were: "recurr*", "repeat*", "repetitive", "frequent*", and "cyclic*". Urinary tract-related terms were: "bladder*", "genitourin*", "genito urin*", "kidney*", "pyelo*", "renal*", "ureter*", "ureth*", "urin*", "urolog*", "urogen*", and "urinary tract*". Infection-related terms were: "infect*", "bacteria*", "microbial*", "sepsis*", and "inflam*". Our search identified 2799 articles, and research shows that rUTIs in women are common and result in substantial patient morbidity and health-care use. When behavioural and non-antibiotic interventions are ineffective, then prophylactic antibiotics are often used to prevent recurrence. The risk of developing antibiotic resistance because of this strategy has been shown in paediatric populations, but evidence in adults remains scarce. Additionally, data on the absolute risk of antibiotic resistance following prophylactic antibiotic use are lacking. To support shared decision making between patients and health-care professionals, robust evidence on both the benefits and risks is, therefore, needed.

Added value of this study

Using electronic health record data from the Secure Anonymised Information Linkage Databank, we emulated a pragmatic trial comparing the initiation of prophylactic antibiotics versus non-initiation in women with rUTIs, focusing on the development of antibiotic resistance. To our knowledge, this is the first target trial emulation, and largest cohort study, to address this question in this population. We calculated absolute risk differences as well as numbers needed to harm, which are useful data for shared decision making.

Implications of all the available evidence

Our findings are consistent with existing knowledge that prophylactic antibiotic use increases the risk of antibiotic resistance in uropathogens. However, we provide important new evidence on the absolute risks of uropathogen antibiotic resistance associated with prophylactic antibiotic use in women with rUTIs. This knowledge is particularly relevant given growing global concerns about antimicrobial resistance. These data are essential to inform shared decision-making discussions between patients and clinicians regarding rUTI prevention strategies.

through a randomised trial. However, a trial would be unethical (if antibiotic resistance was the primary outcome), require a large sample size and long follow-up times, and incur considerable costs. In these circumstances, careful observational research can be used. The target trial framework aims to mimic the design of a randomised trial, addressing common methodological problems that can arise with observational studies, and has been shown to have similar estimates to trials.[10–12] Using the target trial framework, associated analytical methods, and anonymised individual-level data, we aimed to investigate the effect of prophylactic antibiotic use on the risk of antibiotic resistance for women with rUTIs.

Methods

Study design and population

We did a retrospective cohort study that used the Secure Anonymised Information Linkage (SAIL) Databank. SAIL is ISO27001 certified and the national trusted research environment for Wales, holding anonymised, individual-level, population-scale, linked data sources (appendix p 2).[13] We aimed to emulate a pragmatic clinical trial (appendix p 3) to assess the effect of prophylactic antibiotic initiation versus non-initiation on subsequent antibiotic resistance.

Participants were eligible for inclusion if they met the study eligibility criteria between Jan 1, 2015, and Dec 31, 2020. Inclusion criteria were: available identifiers and good quality linkage fields (anonymised linking field; appendix p 4); recorded as being female in the Welsh Demographic Service Dataset; aged 18 years or older; alive and registered with a general practice contributing data to SAIL during the study period and for at least 12 months before study entry to capture comorbidities; and met the definition of rUTIs. The first record of meeting the rUTI definition and the date the definition was met—ie, the date of the second UTI if they had two UTIs in 6 months—was used as the date of diagnosis (known as the index date).

Exclusion criteria were: current or recent users (within the 12 months preceding study entry) of prophylactic antibiotics for rUTI prevention; pregnant at study entry; and evidence of catheter use before study entry. We excluded women with evidence of catheter use or pregnancy to ensure our cohort reflected women with rUTIs seen by health-care professionals and treated in UK primary care. The rationale for this decision is because current UK clinical guidelines recommend that these patient groups are assessed and treated by specialist secondary care services.[7]

The SAIL Databank Information Governance Review Panel approved the study (project approval number 1169). For the purposes of disclosure control and privacy protection, when counts or differences in counts were small, these were rounded to the nearest ten.

Procedures

Using an encrypted anonymised linking field, we linked multiple data sources, comprising Welsh Longitudinal General Practice data, Patient Episode Database for Wales, Welsh Results Reports Service, Welsh Demographic Service Dataset, and Annual District Death Extract based on the Office for National Statistics mortality register (appendix p 2). This linkage provided individual-level data on demographics, clinical diagnoses, prescriptions, urine microbiology, and hospital admissions. Further details, including code lists, have been reported previously.[4]

We defined rUTIs as two or more acute UTIs within 6 months, or three or more within 12 months.[5] Acute UTIs were defined with read codes (codes for clinical terms in electronic health records) related to a UTI and a UTI-related antibiotic on the same day, or using a UTI-related ICD-10 code during a hospital admission. When more than one acute UTI was coded within a 28-day period, these were considered to represent repeat consultations for the same episode and grouped together.

The exposure of interest was prophylactic antibiotic use with trimethoprim, nitrofurantoin, or cefalexin, based on the National Institute for Health and Care Excellence guidance on rUTI prophylaxis.[7] We excluded amoxicillin due to its wide use for other non-UTI-related infections.

Within the SAIL Databank, we followed up each eligible individual from the index date (earliest date of meeting all the eligibility criteria) until they either had an outcome of interest, were lost to follow-up, died, started a second course of prophylactic antibiotics, completed 52 weeks of follow-up, or reached the administrative end of follow-up (Dec 31, 2020).

Outcomes

The primary outcome was hospital admission with an antibiotic-resistant infection by 52 weeks. This was ascertained with ICD-10 codes recorded in hospital admission data in the Patient Episode Database for Wales. The primary outcome was met irrespective of the position of the UTI ICD-10 code in the list of diagnoses. Codes had to occur within 2 days of admission and not within 3 days of a previous admission (appendix p 6), to avoid including transfers between hospitals as new admissions.

Secondary outcomes were hospital admission with an antibiotic-resistant urine infection, evidence of antibiotic resistance to at least one antibiotic on urine culture, and evidence of antibiotic resistance to two or more antibiotics on urine culture (multidrug resistance). To define antibiotic resistance on urine culture, we identified uropathogen resistance to: trimethoprim, nitrofurantoin, cefalexin, amoxicillin, pivmecillinam, fosfomycin, ciprofloxacin, and co-amoxiclav in the Welsh Results Reports Service.[14,15]

Statistical analysis

For categorical variables, number (%) was used to summarise sociodemographic and clinical characteristics, and mean (SD) or median (IQR) was used for continuous variables. We used a grace period for this study—ie, the time after study entry for participants to initiate prophylactic antibiotics.[11,16] The grace period used was 12 weeks and was based on clinical knowledge and previous research showing that a substantial proportion of women who meet the rUTI definition and start prophylaxis do so within this time.[4,11,16] A grace period was used for two reasons. First, when a patient meets the definition of rUTIs and becomes potentially eligible to start prophylaxis, they will (by definition) have an acute UTI. Therefore, they are unlikely to immediately initiate prophylaxis. Second, the Welsh Longitudinal General Practice contains prescribing data only, not dispensing data, and so a single acute antibiotic prescription cannot be distinguished from initiation of prophylactic antibiotics. We defined prophylaxis use as three consecutive prescriptions for either trimethoprim, nitrofurantoin, or cefalexin.

Due to the grace period and prophylaxis being defined after three antibiotic prescriptions, the treatment strategy a participant was assigned and following at the index date (or time zero) could not be defined. To account for this design, and to avoid immortal time bias, we used the methods of cloning, censoring, and weighting.[10,11] In brief, we first made copies (cloning) of each participant, and each copy (clone) was assigned to both treatment strategies at the index date. At weekly time intervals, we assessed whether clones were adherent to their assigned treatment strategy. Clones were censored if they deviated from their assigned strategy (appendix pp 6, 14). Because artificial censoring can introduce selection bias, inverse probability weighting was used to create time-varying stabilised weights for each clone remaining uncensored, estimated with a pooled logistic regression model.[10,11] The weights were also used to adjust for covariates at the index date (ie, age) or before this date (appendix p 3). Continuous variables within the model (age, general practice antibiotic prescribing rate, UTI-related hospitalisations, general practice diagnosed and treated UTIs, and follow-up time) were included as linear and quadratic terms to allow for the possibility of non-linear relationships. Weights were truncated at the 99·95% percentile to reduce the influence of extreme outliers.[17] We assessed imbalance of baseline confounders between treatment strategies at the end of the grace period. Detailed information on how comorbidities were defined and time scales used have been published before.[4]

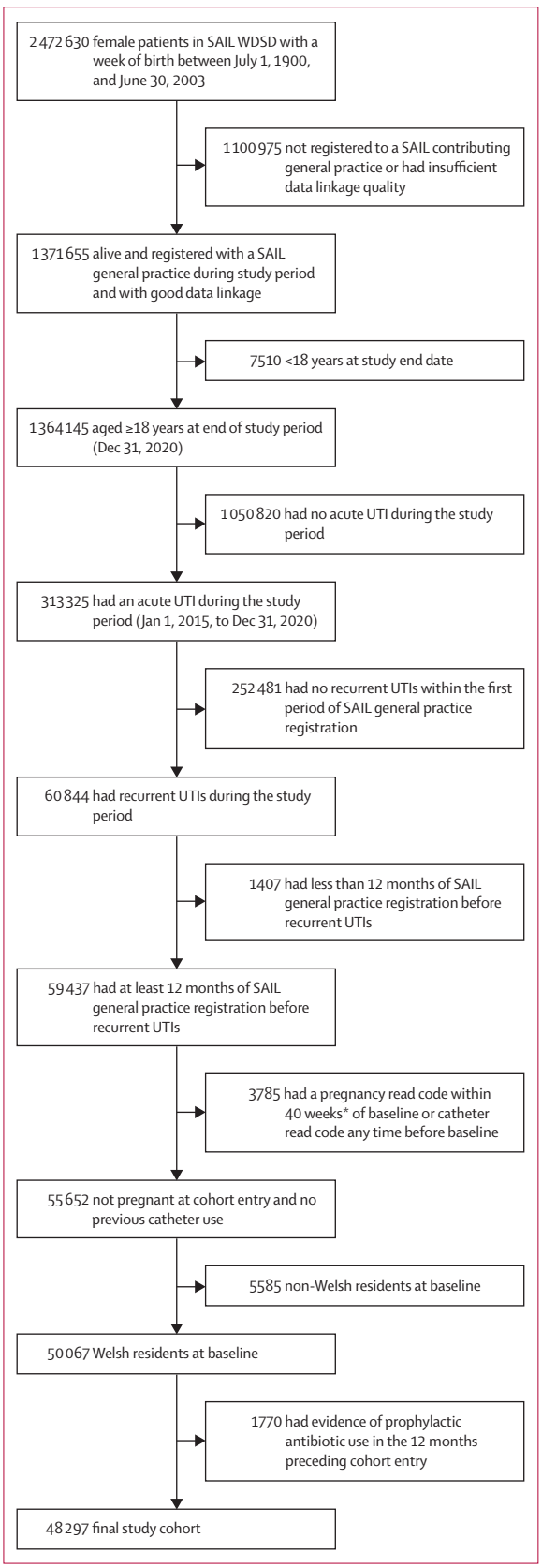

Figure 1: **Cohort profile**
SAIL=Secure Anonymised Information Linkage. UTIs=urinary tract infections. WDSD=Welsh Demographic Service Dataset. *Pregnancy read codes recorded for individuals aged 55 years or older at time of pregnancy event are assumed to be a coding error; these individuals are therefore retained within the project cohort.

Identification of potential confounders was informed by a directed acyclic graph (DAG), representing assumed causal relationships with the exposure and outcome. Using this DAG, we identified a minimal adjustment set, which is defined as a minimal collection of variables that require adjustment to close any confounding paths, based on the assumptions encoded within the DAG. This adjustment enables an unbiased estimate of the effect of prophylactic antibiotics on antibiotic resistance (appendix pp 4, 12 for the DAG, how it was developed, and the minimal adjustment set). Adjusting for more than the minimum adjustment set risks introducing bias by adjusting for colliders (variables that are common effects of two other variables) or mediators. Potential confounders included frailty, general practice antibiotic prescribing rate, immunosuppression, diabetes, social deprivation, UTI-related hospitalisation and general practice diagnosed and treated UTIs in the 12 months before the index date, evidence of a urinary tract stone, evidence of a urinary tract abnormality, the result of the most recent urine culture before the index date, and evidence of antibiotic resistance in the 12 months before the index date (appendix pp 5, 13). Ethnic group was a potential confounder based on our DAG, but was missing in 33% of individuals. Imputing ethnic group did not substantially impact the treatment weights or the results for the primary outcome. Therefore, ethnic group was not included in the final analysis model (appendix pp 7, 15).

We estimated the risk of each outcome by 52 weeks using survival curves with a weighted Kaplan–Meier estimator.[18,19] Using the survival probabilities, we calculated the risk, risk ratio, risk difference, and number needed to treat (NNT) of each outcome for each treatment strategy by 52 weeks. We refer henceforth to the NNT as the NNT for one additional patient to benefit or be harmed (NNTH), to help when presenting the 95% CIs for this effect estimate when it spans both harm and benefit.[20] Cumulative incidence plots were derived from the risks. To prevent disclosure of individuals due to small numbers, the cumulative incidence curves are based on a rolling average. To calculate the 95% CIs for each estimate, we used a non-parametric bootstrap with 500 bootstrap replicates.

Exploratory analyses were done to assess whether any observed differences between exposure groups could be accounted for by differences in competing events or urine culture sampling. We compared competing events (eg, death) between treatment strategies. We also compared the characteristics of women who initiated prophylactic antibiotics within the grace period and who, thus, entered the antibiotic prophylaxis group with the patients who initiated prophylactic antibiotics after the grace period and entered the no antibiotic prophylaxis group. Finally, for the outcome of antibiotic resistance on urine culture, we explored how many participants (and relative proportions) in each study group had a urine

culture reported within 7 days of a treated UTI after the 12-week grace period.

Pre-planned subgroup analyses, stratified by frailty level, were done to explore whether the risk of antibiotic resistance changed according to frailty level, since individuals with increasing frailty are more susceptible to the adverse effects of antibiotics. We grouped moderate and severe frailty subgroups for several reasons: individuals with moderate or severe frailty have substantially higher rates of hospital admission and mortality than do lower frailty groups; they are the two frailty groups targeted for identification and intervention in UK primary care; and there were low numbers within the severe frailty category.[21,22] Subgroup analyses were done for the two outcomes related to antibiotic resistance on urine culture only, as the outcomes of hospital admission with a resistant infection and resistant urine infection were both rare (less than 2%). To assess whether the effect of prophylactic antibiotics differed between subgroups, we calculated the difference in risk difference between each subgroup and used a non-parametric bootstrap with 500 bootstrap replicates of the original study population, stratified by frailty level, to estimate the 95% CIs. We did sensitivity analyses adjusting for loss to follow-up to assess the impact on our estimates and used E-values. The E-value quantifies the minimum strength of association on the risk–ratio scale that any potential unmeasured confounder would need to have with both the exposure (prophylactic antibiotics) and the outcome (antibiotic resistance), after accounting for the covariates included in the analysis model, to reduce the observed effect to the null.[23] Best practice for reporting E-values is to report both the E-value for the point estimate and the confidence interval closest to the null. The E-value for the confidence interval closest to the null quantifies the minimum strength of association that an unmeasured confounder would need to have with both the exposure and the outcome to shift it to include the null value.[23]

We used R version 4.1.3 for all analyses described. The STROBE checklist was used to guide reporting (appendix pp 8–9).[24]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From nearly 2·5 million women in the SAIL Databank, 48 297 women were included in our target trial emulation based on meeting the eligibility criteria between Jan 1, 2015, and Dec 31, 2020 (figure 1, table 1). At the end of the 12-week grace period and before adjustment, compared with the non-antibiotic prophylaxis group the antibiotic prophylaxis group were older (71·0 years *vs* 59·0 years), frailer (n=580 [69·9%] were mild to severely frail *vs* n=24760 [55·8%]), more likely to have

	Total population (n=48 297)
Median age at study entry, years (IQR)	60·0 (39·0–76·0)
Ethnic group	
White	31 443 (65·1%)
Mixed	115 (0·2%)
Asian	353 (0·7%)
Black	135 (0·3%)
Other	187 (0·4%)
Missing data	16 064 (33·3%)
Deprivation quintile (WIMD)	
1 (most deprived)	10 021 (20·7%)
2	9621 (19·9%)
3	9589 (19·9%)
4	9231 (19·1%)
5 (least deprived)	9835 (20·4%)
Mean BMI, kg/m² (SD)*	27·80 (6·95)
Smoking status	
Never smoked	18 747 (38·8%)
Ex-smoker	19 739 (40·9%)
Current smoker	7388 (15·3%)
Missing	2423 (5·0%)
Alcohol status	
Non-drinker	17 701 (36·7%)
Current drinker	22 654 (46·9%)
Excess drinker	1316 (2·7%)
Missing	6626 (13·7%)
Frailty (eFI)[22]	
Fit	20 655 (42·8%)
Mild frailty	16 838 (34·9%)
Moderate frailty	7678 (15·9%)
Severe frailty	3126 (6·5%)
Diabetes	11 529 (23·9%)
Chronic kidney disease	6313 (13·1%)
Dementia	2617 (5·4%)
Immunosuppression	2746 (5·7%)
Urinary tract stone	227 (0·5%)
Urinary tract structural abnormality	699 (1·4%)
Evidence of uropathogen antibiotic resistance on urine culture in the 12 months before study entry	16 032 (33·2%)
Median total urinary tract infections in the 12 months before study entry (IQR)	2 (2–3)
Most recent culture result in the 12 months before study entry	
No growth	15 207 (31·5%)
Growth of 1–2 organisms	17 704 (36·7%)
Mixed or heavy mixed growth	4894 (10·1%)
No recent sample	10 492 (21·7%)
Median total follow-up time, days (IQR)	365 (365–366)

Data are n (%), unless otherwise stated. The population was cloned at baseline. eFI=electronic frailty index. WIMD=Welsh Index of Multiple Deprivation. *No data for 15 323 women.

Table 1: **Baseline characteristics**

	Risk in non-antibiotic prophylaxis group, % (95% CI)	Risk in antibiotic prophylaxis group, % (95% CI)	Risk ratio (95% CI)	Risk difference, % (95% CI)	NNTH (95% CI)
Primary outcome					
Hospital admission with an antibiotic-resistant infection	1·4% (1·3–1·5)	1·9% (1·0–3·1)	1·41 (0·74–2·24)	0·6% (–0·4 to 1·7)	177·3 (NNTB 2037·6 to infinity to NNTH 2281·9)
Secondary outcomes					
Hospital admission with an antibiotic-resistant urine infection	1·2% (1·1–1·3)	1·8% (0·9–3·0)	1·56 (0·76–2·49)	0·7% (–0·3 to 1·8)	150·9 (NNTB 1514·5 to infinity to NNTH 1281·4)
Antibiotic resistance to one or more antibiotics on urine culture	23·7% (23·4–24·2)	30·6% (27·2–34·3)	1·29 (1·14–1·44)	6·9% (3·3 to 10·5)	14·6 (9·5 to 30·5)
Antibiotic resistance to two or more antibiotics on urine culture	14·0% (13·8–14·4)	22·0% (19·1–25·3)	1·57 (1·37–1·79)	8·0% (5·1 to 11·1)	12·5 (9·0 to 19·5)

NNTB=number needed to be treated for one additional patient to benefit. NNTH=number needed to be treated for one additional patient to be harmed.

Table 2: **Study outcomes**

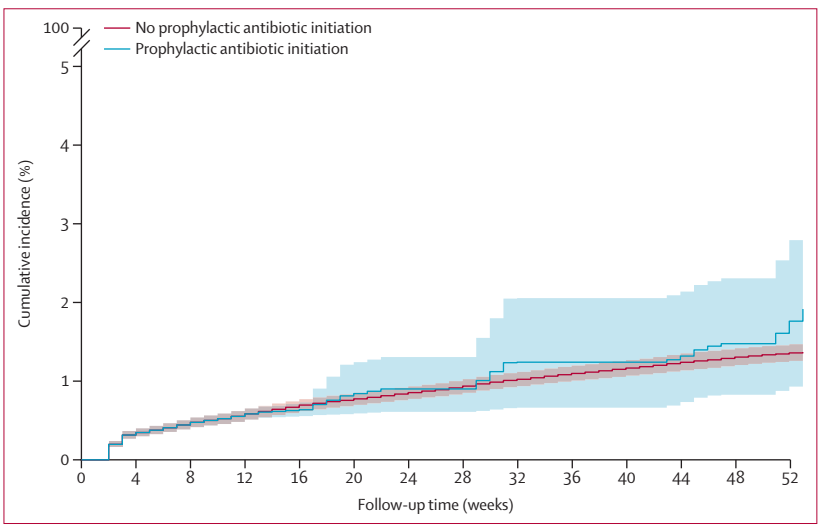

Figure 2: **Cumulative incidence of admission with an antibiotic-resistant infection**
Admission is for those who initiate prophylactic antibiotics during the grace period versus those who do not. Follow-up time starts from when participants met the eligibility criteria and entered the study. To prevent disclosure of individuals due to small numbers, the cumulative incidence curves are based on a rolling average. Shaded area is 95% CI.

diabetes (n=240 [28·9%] *vs* n=10 280 [23·2%]), more likely to have bacterial growth on urine culture before the index date (n=450 [54·2%] *vs* n=16 100 [36·3%]), and had evidence of uropathogen resistance before the index date (n=420 [50·6%] *vs* n=14 380 [32·4%]). After inverse probability weighting, covariate balance was reached between groups at the end of the grace period across all outcomes (appendix pp 16–19). The most common antibiotic used during the 12-week grace period (rounded to 840 women to adhere to SAIL disclosure rules) was nitrofurantoin (n=410 [48·8%]), followed by trimethoprim (n=330 [39·3%]), and then cefalexin (n=100 [11·9%]). In fewer than 1·2% of women (n<10), it appeared patients were using more than one antibiotic for prophylaxis.

A total of 839 women initiated prophylactic antibiotics during the grace period, with a median time between the first and last prescription of 78 days (IQR 65–143). Patients who started antibiotic prophylaxis during follow-up but after the grace period (n=2060), and entered the no antibiotic prophylaxis group (exploratory analysis), had similar characteristics to those who started during the grace period (appendix p 10).

616 (1·3%) women were admitted to hospital with an antibiotic-resistant infection by 52 weeks (the primary outcome), with a risk of 1·4% (95% CI 1·3–1·5) in the non-prophylactic antibiotic group and 1·9% (1·0–3·1) in the prophylactic antibiotic group (risk ratio 1·41, 95% CI 0·74–2·24). Absolute risk differences and NNTH are presented in table 2. Figure 2 shows the cumulative incidence curves by group over the 52-week follow-up and, due to the imbalance in treatment group sizes, it also shows that the uncertainty in the treatment effect for the antibiotic prophylaxis group is greater than for the non-antibiotic prophylaxis group. 529 (1·1%) women were admitted to hospital with an antibiotic-resistant UTI (secondary outcome). The risk of admission with an antibiotic-resistant UTI was 1·2% (1·1–1·3) in the non-antibiotic prophylaxis group versus 1·8% (0·9–3·0) in the prophylactic antibiotic group (risk ratio 1·56, 95% CI 0·76–2·49; table 2, appendix p 20).

When a single uropathogen was recorded on urine culture, the predominant uropathogen was *Escherichia coli* (n=7185/10 365 [69·3%]). In total, 10 773 (22·3%) women had antibiotic resistance to at least one antibiotic, and 6393 (13·2%) had resistance to two or more antibiotics, during follow-up. The risk of resistance to one or more antibiotics on urine culture was 23·7% (23·4–24·2) in the non-antibiotic prophylaxis group versus 30·6% (27·2–34·3) in the prophylactic antibiotic group (risk ratio 1·29, 95% CI 1·14–1·44; table 2, appendix p 20). For the outcome of antibiotic resistance to two or more antibiotics

	Risk in non-antibiotic prophylaxis group, % (95% CI)	Risk in antibiotic prophylaxis group, % (95% CI)	Risk ratio (95% CI)	Risk difference, % (95% CI)	NNTH (95% CI)
Antibiotic resistance to one or more antibiotics on urine culture					
Fit	14·6% (14·0–15·1)	20·1% (14·4–25·6)	1·38 (1·00–1·76)	5·5% (–0·1 to 10·9)	18·2 (NNTB 81·6 to infinity to NNTH 136·6)
Mild frailty	24·6% (24·0–25·4)	29·2% (24·4–34·8)	1·19 (0·99–1·42)	4·6% (–0·3 to 10·2)	21·82 (NNTB 167·9 to infinity to NNTH 132·2)
Moderate or severe frailty	41·0% (40·0–42·1)	51·3% (44·7–58·6)	1·25 (1·09, 1·42)	10·3% (3·8 to 17·3)	9·7 (5·8 to 26·5)
Antibiotic resistance to two or more antibiotics on urine culture					
Fit	7·2% (6·8–7·5)	13·4% (9·2–18·4)	1·87 (1·29–2·55)	6·2 (2·1 to 11·1)	16·0 (8·9 to 46·2)
Mild frailty	14·2% (13·7–14·7)	20·5% (16·0–26·7)	1·45 (1·13–1·89)	6·3 (1·9 to 12·5)	15·8 (8·0 to 53·7)
Moderate or severe frailty	27·9% (27·0–28·9)	40·0% (34·2–47·1)	1·44 (1·22–1·69)	12·1 (6·1 to 19·3)	8·3 (5·2 to 16·3)

NNTB=number needed to be treated for one additional patient to benefit. NNTH=number needed to be treated for one additional patient to be harmed.

Table 3: **Subgroup analysis according to frailty**

	Difference in risk differences for antibiotic resistance to one or more antibiotics on urine culture, % (95% CIs)	Difference in risk differences for antibiotic resistance to two or more antibiotics on urine culture, % (95% CIs)
Fit *vs* mild frailty	0·91% (–6·52 to 8·12)	–0·09% (–6·90 to 6·95)
Fit *vs* moderate or severe frailty	–4·80% (–13·46 to 3·25)	–5·86% (–13·94 to 2·09)
Mild frailty *vs* moderate or severe frailty	–5·70% (–13·66 to 2·72)	–5·77% (–13·66 to 2·10)

Table 4: **Risk difference between frailty subgroups**

on urine culture, the risk was 14·0% (13·8–14·4) in the non-antibiotic prophylaxis group versus 22·0% (19·1–25·3) in the prophylactic antibiotic group (risk ratio 1·57, 95% CI 1·37–1·79; table 2, appendix p 21). The proportions of patients with urine culture associated with a UTI (exploratory analysis) were similar between groups (21·7% in the antibiotic group compared with 16·8% in the non-antibiotic group) and so no additional adjustment was done. Pre-planned subgroup analyses showed that, for both risks of antibiotic resistance to at least one antibiotic or to two or more on urine culture, the risk difference did not vary between frailty levels (tables 3, 4).

Adjusting for loss to follow-up increased the risk ratio and risk difference for all outcomes but the difference did not appear clinically meaningful (appendix p 11). For the outcome of antibiotic resistance on urine culture, the E-value for the point estimate was 1·90 and for the confidence interval was 1·54. For the outcome of antibiotic resistance on urine culture to two or more antibiotics, the E-value for the point estimate was 2·52 and confidence interval was 2·08.

Exploratory descriptive analyses of competing events showed they were similar across all outcomes (appendix p 11). For the primary outcome, death during follow-up was similar between those who initiated prophylactic antibiotics during the grace period compared with those who did not (40/839 [4·8%] for the antibiotic initiators *vs* 2740/47 485 [5·8%] for the non-initiators), more women were lost to follow-up in those who did not initiate prophylactic antibiotics during the grace period (n<10 [<1·2%] for the antibiotic initiators *vs* n=1300 [2·7%] for those who did not), and starting a second course of prophylactic antibiotics was more common in those who initiated prophylactic antibiotics during the grace period (n=210 [25·0%] for antibiotic initiators *vs* n=310 [0·7%] for those who did not during the grace period; appendix p 11).

Discussion

This retrospective cohort study used the target trial framework to investigate the effect of prophylactic antibiotic use on the risk of antibiotic resistance for women with rUTIs. We found no evidence that prophylactic antibiotic use in women with rUTIs increased the risk of hospital admission with an antibiotic-resistant infection or antibiotic-resistant urine infection. However, the risk of antibiotic resistance of a cultured uropathogen increased with prophylactic antibiotic use with a NNTH of 14·6 (95% CI 9·5–30·5) for resistance to at least one antibiotic on urine culture and a NNTH of 12·5 (9·0–19·5) for resistance to two or more antibiotics on urine culture. We found no conclusive evidence of a subgroup effect by frailty level.

Evidence for the impact of prophylactic antibiotics on the development of antibiotic resistance is scarce in children and adults. In children, clinical trial data suggest that prophylactic antibiotic use increases the risk of a subsequent antibiotic-resistant infection (risk ratio 2·40, 95% CI 0·62–9·26).[25] One trial in adults who

intermittently self-catheterise showed an increased risk of antibiotic resistance with prophylactic antibiotic use.[26] This increased risk has also been shown in two trials in women with rUTI.[27,28] Our findings broadly agree with the findings from all these studies, although our estimated risk ratio is lower than that estimated in children.

A matched cohort study done in Canada in older (≥66 years) adults reported that antibiotic prophylaxis increased the risk of antibiotic resistance (hazard ratio 1·31, 95% CI 1·18–1·44), especially to the antibiotic prescribed (2·01; 1·80–2·24).[29] We found similar results, in that users of prophylactic antibiotics had higher rates of resistance; however, we found higher rates of resistance in both users and non-users of antibiotics. This difference could be due to several factors. First, we did not restrict our population to patients with positive urine culture since culture is thought to miss a proportion of UTIs. Secondly, we only included women with rUTIs and thus our population is more likely to have been exposed to repeated UTI-related antibiotics and potentially have higher rates of resistance. Finally, the differences could be related to the different study populations based on sex and age.

To our knowledge, this is the first study to estimate the absolute risk of antibiotic resistance with prophylactic antibiotic use in women with rUTIs in the UK. This study provides valuable information for policy makers developing guidelines for prophylactic antibiotic use, but most importantly for discussions between patients and clinicians in primary care about rUTI prevention. To enable true shared decision making, information of the risks and benefits of all treatment options should be available. The benefit of antibiotic prophylaxis on reducing the risk of UTI recurrence is well established.[8,27] Despite evidence of an increased risk of antibiotic resistance with prophylactic antibiotic use, the degree of risk has not been previously quantified in adults. Our study provides new evidence to inform shared decision-making discussions about rUTI prevention.

Our study has several strengths. We used a large sample of women with rUTIs from electronic health records, reflecting the populations of women with rUTIs seen in clinical practice. We developed a DAG and a minimal adjustment set to account for important potential confounders for this analysis. We also used the target trial framework to avoid methodological biases in our design and analysis.

Our study also has potential limitations. Due to the use of observational data, residual confounding is possible. We identified important potential confounders through developing a DAG based on the literature and clinical expertise to minimise this risk. We defined prophylactic antibiotic use as three consecutive prescriptions for the same antibiotic, and so potentially we could have included acute, rather than long-term, use. However, this misclassification is probably small as a UTI is unlikely to be acutely treated repeatedly with the same antibiotic over a 90-day period. Additionally, women who rotate prophylactic antibiotics or stopped prophylaxis before the third prescription were probably misclassified as non-users. If this occurred, the results would probably be pushed towards the null. Due to the pragmatic design of this study, patients who start antibiotic prophylaxis after the grace period entered the no prophylactic antibiotic group. Again, this design likely pushes the result towards the null. Study participants included individuals diagnosed with rUTIs in 2020, a year during which the COVID-19 pandemic and associated disruptions to health care might have influenced our estimates. However, only 11·6% of participants entered the study at the beginning of 2020, suggesting that any impact from the pandemic is likely to be minimal. For secondary outcomes related to antibiotic resistance of a cultured uropathogen, we did not restrict to new uropathogen antibiotic resistance. However, we did adjust for history of uropathogen antibiotic resistance in the 12 months before the index date. Finally, not all urine cultures will have cultured an organism (and, therefore, undergone antibiotic susceptibility testing) nor been screened for antibiotic resistance to all antibiotics, including in our analysis, due to selective testing. These factors possibly result in an underestimation of antibiotic resistance.

Our study quantifies the increased risk of antibiotic resistance with prophylactic antibiotics use. Further research in other populations, especially in terms of ethnic group, would be beneficial to our understanding of the risk of antibiotic resistance with prophylaxis and generalisability. What remains unclear is how this risk of antibiotic resistance develops over time, with differing durations of prophylaxis. Most research has examined prophylactic antibiotic use for up to 12 months and guidelines recommend treatment for 3–6 months. In clinical practice, and in response to the preferences of many women, antibiotics can be used for longer periods. Therefore, future research should try to establish the risks of longer-term use to inform policy.

In conclusion, this retrospective observational study of the risk of antibiotic resistance with antibiotic prophylaxis for rUTIs showed that the risk of admission with a resistant infection and resistant urine infection is similar to that of non-users, whereas the risk of uropathogen antibiotic resistance on urine culture increased with prophylactic antibiotic use. These findings have considerable implications for clinical practice and policy and allow for more informed discussions around prophylactic antibiotic use, enhancing shared decision making in this field.

Contributors

LS, HA, AE, FW, and RC-J contributed to study conceptualisation. VB, AA, and LS were responsible for data curation. LS, VB, DF, and SS did the formal analysis and contributed to the investigation. LS, HA, RC-J, DF, SS, and GH were responsible for methodology. LS, HA, AE, FW, and RC-J acquired funding and contributed to project administration. LS, HA, AE, FW, GH, and RC-J contributed to interpretation. LS wrote the original draft, and LS, HA, VB, AA, AE, FW, RC-J, DF, SS, and GH reviewed and edited revisions. LS, VB, HA, DF, AA, and RC-J had full access to the

study data within the SAIL Databank. All authors accept responsibility for submission of this study for publication.

Declaration of interests

GH has received urinary tract infection diagnostic devices loaned from Llusern Scientific, GADx, and Sysmex Astrego for the purposes of research. AE declares royalties from Oxford University Press for the *Oxford Handbook of Shared Decision Making* (now 4th edition, 2025), payment from the UK Covid-19 Inquiry for an expert report on general practice, being an advisor to the Centre for Shared Decision Making (University of Southern Denmark, Odense, Denmark), and being an academic member of the Royal College of General Practitioners, Welsh Council. All other authors declare no competing interests.

Data sharing

The data used in this study are available in the Secure Anonymised Information Linkage (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 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 code for preparing and analysing the data is available on GitHub: https://github.com/SwanseaUniversityDataScience/ImPART_Target_Trial.

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