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Effect of methenamine hippurate shortage on antibiotic prescribing for urinary tract infections in Norway—an interrupted time series analysis

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Background: Despite a lack of conclusive evidence of effect, methenamine hippurate is widely prescribed as preventive treatment for recurrent urinary tract infections (UTIs) in Norway. A national discontinuation of methenamine hippurate treatment due to a 4-month drug shortage in 2019 presented an opportunity to evaluate its preventive effect on UTIs among regular users.

Objective: To estimate the impact of the methenamine hippurate drug shortage on prescription frequency of UTI antibiotics.

Methods: Data from The Norwegian Prescription Database was analysed using an interrupted time series design. The time series consisted of 56 time periods of 14 days. The model included two naturally occurring interruptions: (i) the methenamine hippurate drug shortage, and (ii) reintroduction of the drug. The study population were 18 345 women ≥50 years receiving ≥2 prescriptions of methenamine hippurate in the study period before the shortage. Main outcome measure was number of prescriptions of UTI antibiotics per 1000 methenamine hippurate users. Prescription rates of antibiotics for respiratory tract infections were analysed to assess external events affecting antibiotic prescribing patterns.

Results: We found a significant increase of 2.41 prescriptions per 1000 methenamine hippurate users per 14-day period during the drug shortage (95%CI 1.39, 3.43, $P<0.001$), followed by a significant reduction of −2.64 prescriptions after reintroduction (95%CI −3.66, −1.63, $P<0.001$).

Conclusions: During the methenamine hippurate drug shortage, we found a significant increase in prescribing trend for UTI antibiotics followed by a significant decrease in prescribing trend after reintroduction. This change in trend seems to reflect a preventive effect of the drug on recurrent UTIs.

Introduction

Urinary tract infections (UTIs) are common and burdensome infections among women, with increasing disease burden with age.[1] Extensive use of antibiotics over time has altered the susceptibility of urinary bacteria leading to an increase in antimicrobial resistance (AMR).[2] AMR is an evolving worldwide problem threatening future possibilities to treat simple infections.[3] To slow down the progression of AMR, it is important to explore non-antibiotic preventive treatment strategies. Methenamine hippurate, a urinary antiseptic, has been used as preventive treatment for recurrent UTIs in Norway for nearly 50 years.[4] The drug is distributed to several countries,[5] although the classification of the drug varies. In some countries (e.g. Australia), it is possible to obtain the medicine without a doctor's prescription.[6] However, while other non-antibiotic preventive options such as cranberry products, ascorbic acid (except infusions) and D-mannose are available over the counter in Norway, methenamine hippurate is a prescription-only drug. Although non-inferiority to low dose urinary antibiotics have recently been demonstrated,[7] conclusive evidence of long-term effect is lacking. Consequently, the Norwegian antibiotic guideline only suggests use of this drug

when other preventive measures are ineffective.[8] Despite this, the drug is widely prescribed by Norwegian physicians, possibly due to the favourable side effect profile,[9] it being neutral in terms of driving AMR and the lack of other effective non-antibiotic preventive drugs.[10] Although methenamine hippurate is a urinary antiseptic, the drug is grouped with antibiotics in the Anatomical Therapeutic Chemical (ATC) classification system.[11] Methenamine hippurate constituted as much as 26% of the total sale of antimicrobial agents in Norway in 2021, measured in defined daily dosages (DDD).[12]

In 2019 there was a drug shortage of methenamine hippurate from the supplier. In Norway, the shortage persisted from January 2019 through April 2019,[13] resulting in a national discontinuation of methenamine hippurate treatment. This national discontinuation presented an opportunity to evaluate the effect of methenamine hippurate on the prescription rate of UTI antibiotics in a population of regular users. Using an interrupted time series design, we aimed to explore the impact of methenamine hippurate drug shortage on prescriptions of urinary antibiotics for female methenamine users ≥50 years. Our hypothesis was that the drug shortage would lead to increased prescription trend of UTI antibiotics, and that reintroduction of the drug after the shortage would lead to a decreased prescription trend in the same population. The changes in prescription rate of urinary antibiotics are assumed to reflect changes in the rate of UTIs in this population.

Materials and methods

Ethics

The study was presented for the Norwegian Ethical Committee (REK southeast B, 2020/138648) that granted exemption from consent. Data management and safety was approved by the Norwegian Centre for Research Data (NSD, now Sikt, ref. 449273).

Study design

Interrupted time series analysis (ITSA) is a quasi-experimental study design well suited to investigate the effects of defined population-level interventions where randomized controlled trials (RCTs) are not feasible.[14] It can be particularly valuable for assessing the impact of abrupt external events, beyond the confines of a controlled experiment, on specific outcomes of interest. In this study, we took advantage of a time-limited national drug shortage of methenamine hippurate to retrospectively evaluate the effect of the shortage on UTI antibiotic use in our study population. We used an ITSA design with a non-equivalent control group.[15] The non-equivalent control was a time series of prescriptions of antibiotics for respiratory tract infections (RTI antibiotics) in the same study population and time period. We used this time series to exclude that any change in prescribing trend of UTI antibiotics reflected a general shift in antibiotic prescribing habits of Norwegian physicians during the study period. The prescribing trend for RTI antibiotics adjusted for seasonality should not be affected by the methenamine hippurate drug shortage. There are currently no official and unified reporting guidelines for time series studies.[16,17] In the absence of a specific checklist, the STROBE statement was used.[18]

Study population

Our original data extract contained data on all people ≥18 years who had received ≥1 prescription of methenamine hippurate in the period 1 January 2015–30 April 2020. Based on national prescription overviews, we knew that most methenamine hippurate users in Norway were older women. As the aetiology and/or treatment indication for UTI during pregnancy differ, we set the cut off at 50 years to make sure that no women in our material were pregnant. Participants with a registered death date were excluded from the dataset, leaving all participants continuously enrolled for the whole study period. Finally, we limited our study population to women ≥50 years who had received ≥2 prescriptions of methenamine hippurate in the study period before the drug shortage. A flow chart of participant inclusion is presented in Figure 1.

Naturally occurring events under study

Our study period was from 15 January 2018 to 8 March 2020. This study period was interrupted by two naturally occurring events. The first interruption was the methenamine hippurate drug shortage, starting from the issuance of the warning of shortage from The Norwegian Medicines Agency on 15 January 2019, and the second interruption was the reintroduction of the drug to the market, starting from the cancellation of the warning issued 26 April 2019.[13] Methenamine hippurate is not available over the counter and is prescribed in boxes of 100 tablets. The preventive dose is 1 g×2 (two tablets), which means that one box is enough for 50 days of treatment.[9] At the time of the drug shortage, the participants would have different amounts of tablets left from their most recent dispensed prescription. We assumed that the drug shortage would have immediate effect only for participants approaching prescription renewal, and that the number of participants running out of medication would increase throughout the shortage period. Likewise, we assumed it would take some time after the shortage before all participants had collected their methenamine hippurate prescriptions. As there are no studies yet to determine any possible long-term preventive effect of this drug after terminating treatment, nor number of days before full effect after restarting the drug, we chose not to include a wash-out period in our main analysis.

Outcome measure

Primary outcome measure was number of prescriptions of urinary antibiotics per 1000 methenamine hippurate users per 14 days. The rate of prescriptions was considered to reflect the rate of UTIs in this population.

Selection of antibiotics

We defined UTI antibiotics as the first-choice drugs for acute cystitis in the Norwegian guidelines: pivmecillinam, nitrofurantoin and trimethoprim. These are by far the most used antibiotics for cystitis in Norway and make up 82.8% of all antibiotic prescriptions for cystitis in general practice for all ages, and 80.3% for the age group ≥50 years.[19] We excluded prescriptions ≥14DDD to avoid including any preventive antibiotic treatment. We defined RTI antibiotics as phenoxymethylpenicillin, erythromycin and doxycycline. Prescriptions of amoxicillin, ciprofloxacin and trimethoprim/sulfamethoxazole were all omitted because of dual indications (UTI/RTI). Prescription rates of preventive antibiotic treatment and the broad-spectrum UTI antibiotics trimethoprim/sulfamethoxazole and ciprofloxacin were all found to be low in our study population. An illustrative graph is provided in Supplementary data, Figure S1 (available as Supplementary data at *JAC* Online). The exclusion of amoxicillin from our selection of RTI antibiotics was justified because this non-equivalent control was included to uncover any general change in prescription habits/trends of Norwegian physicians during the methenamine shortage. A general change in prescribing trends should be apparent even when only looking at a selected number of RTI antibiotics.

Dataset

The dataset was obtained from The Norwegian Prescription Database (NorPD).[20] Norwegian pharmacies register all prescriptions electronically. The study dataset contained all prescriptions in ATC class J01 'Antibiotics

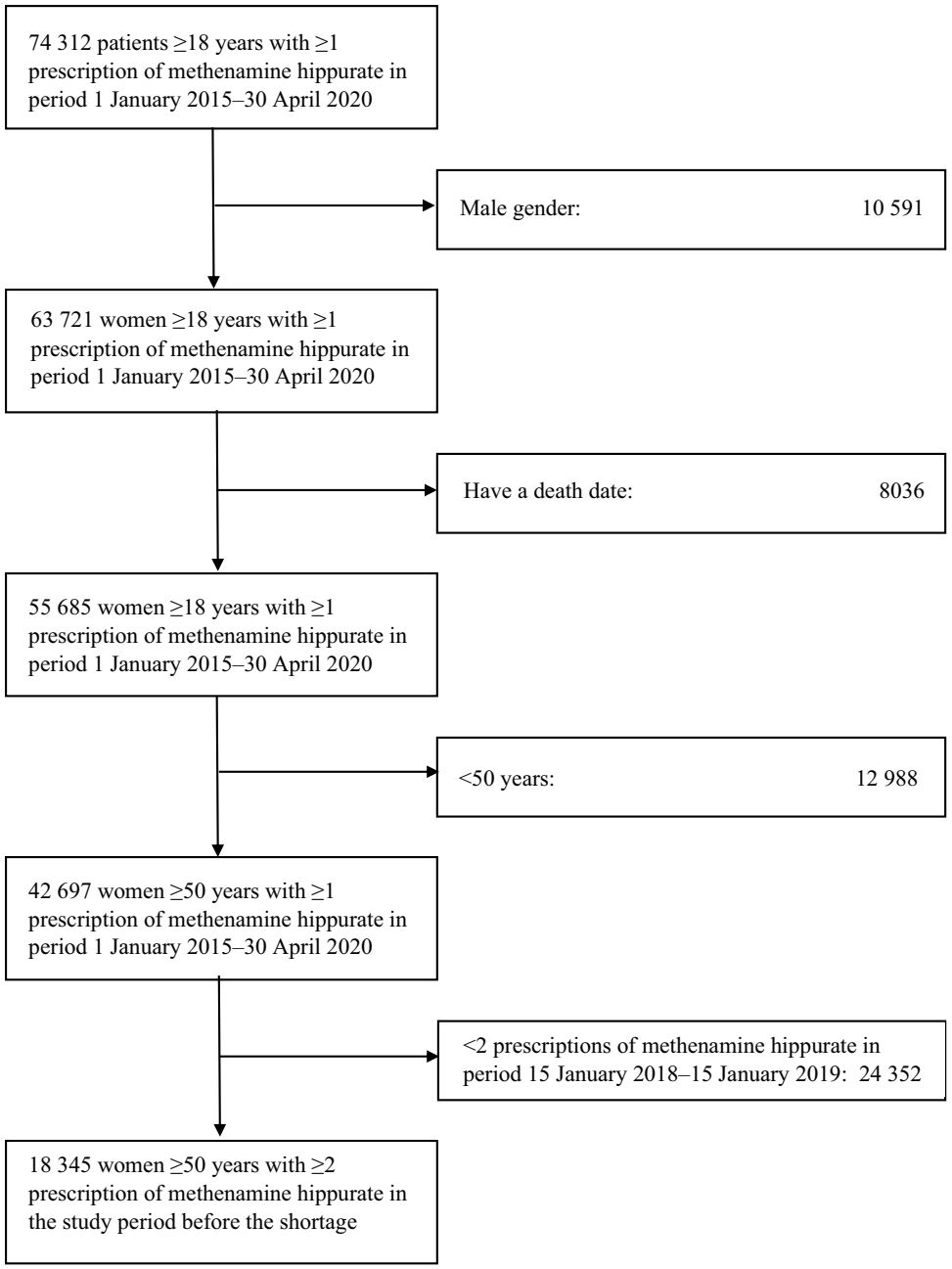

Figure 1. Flow chart of participant inclusion.

for systemic use', as well as date of birth, death date, gender and prescriptions for medication to treat conditions that increase the risk of recurrent UTIs; ATC-A10/diabetes medication, ATC-G03CA/oestrogens and ATC-G04BD/medication for incontinence/bladder disfunction.[21] Our dataset spanned over 56 time periods. Each period was 14 days. The drug shortage started in period 27, and reintroduction in period 34.

Statistical analysis

An ITSA involves studying a single unit of interest. The outcome variable is ordered in consecutive and equally spaced time periods. The intervention(s) under study are assumed to interrupt the level and/or trend of the series.[22] For our model, we defined the methenamine hippurate drug shortage as 'intervention 1' and the reintroduction of the drug as 'intervention 2'. All statistical analysis were performed using STATA 17 software. The time series were analysed by the 'itsa newey' command, which performs an ordinary least squares regression (OLS) with Newey–West standard errors to correct for autoregression and heteroskedasticity. To ensure a fitted model accounting for correct autocorrelation structure, we used the actest command (Cumby–Huizinga test for autocorrelation),[23] as well as autocorrelation function and partial autocorrelation function of the residuals.

Table 1. Table of characteristics of the study population

Number of prescriptions of methenamine hippurate before shortage	Number of participants (%)	Age (years) median (IQR[a])	≥1 prescription diabetes medication: number (%)	≥1 prescription incontinence medication: number (%)	≥1 prescription oestrogen medication: number (%)
2	3630 (19.8)	73 (64–81)	213 (5.9)	211 (5.8)	497 (13.7)
3	4524 (24.7)	73 (66–81)	246 (5.4)	273 (6.0)	568 (12.6)
4	4067 (22.2)	74 (67–82)	239 (5.9)	200 (4.9)	430 (10.6)
5	1667 (9.0)	74 (66–81)	65 (3.9)	75 (4.5)	182 (10.9)
6	1045 (5.7)	74 (66–82)	46 (4.4)	43 (4.1)	113 (10.8)
≥7	3412 (18.6)	83 (74–89)	242 (7.1)	209 (6.1)	141 (4.1)

[a]Interquartile range.

For the single ITSA with two 'interventions' we used the following model:[24]

$$Y_t = \beta_0 + \beta_1 T_t + \beta_2 X_{1t} + \beta_3 X_{1t} T_{1t} + \beta_4 X_{2t} + \beta_5 X_{2t} T_{2t} + \epsilon_t$$

Y_t is the sum of the outcome variable measured at equally spaced time points, *t*. T_t represents the time since start of the study, X_{1t} is a dummy variable for the methenamine hippurate shortage and X_{2t} is a dummy variable for the methenamine hipprate reintroduction. For both, the time periods before the change were coded 0, otherwise 1. $X_{1t}T_{1t}$ and $X_{2t}T_{2t}$ are the corresponding interaction terms of interest. β_0 represents the starting level of the outcome variable, whereas β_1 is the trend in the time periods preceding the drug shortage. β_2 represents the level change of the outcome in the first time period immediately after the start of the shortage, and β_3 the difference in trend in the time periods before and during the shortage. β_4 represents the level change of the outcome in the time period immediately after methenamine hippurate reintroduction, and β_5 the difference between the trend during the shortage and after reintroduction. Immediate level changes in the first time period after the start of the shortage and after reintroduction, manifesting as significant *P* values for β_2 and β_4. However, in this study, we were mostly interested in the effect of the drug shortage over time, manifesting as significant *P* values for β_3 and β_5.

We used the same approach for an ITSA for RTI antibiotics for the comparison series. RTI antibiotics exhibit a seasonal pattern peaking in the winter season. We added an independent variable that assumed the value of 1 for all time periods in winter season (October–March) and 0 for all other time periods. The variable was added to the RTI model as a covariate to adjust for seasonality. The final models were adjusted for autocorrelation with the lags of 0 (UTI antibiotics) and 4 (RTI antibiotics).

For sensitivity analysis, we performed the ITSA (i) for women ≥45 years with ≥2 methenamine hippurate prescriptions in the study period before the drug shortage, (ii) for women ≥50 years with ≥2 methenamine hippurate prescriptions both before and after the drug shortage, (iii) for women ≥50 years with ≥3 methenamine hippurate prescriptions before the drug shortage, (iv) for women ≥50 years with ≥4 methenamine hippurate prescriptions before the drug shortage, and (v) the main ITSA with a wash-out period of one time period after each of the two time series interruptions.

Results

Descriptive results

Our study population consisted of 18 345 women with a mean age of 74.6 (SD 11.3) with median age 75 and interquartile interval 67, 83. Of the women, 1044 (5.7%) had received at least one prescription for diabetes medication, 1008 (5.5%) at least one prescription for incontinence/bladder dysfunction medication and 1933 (10.5%) at least one prescription for oestrogen treatment. Table 1 shows characteristics of the study population, Figure 2 shows monthly prescriptions of methenamine hippurate for our study population from 2015 to 2020.

ITSA of prescriptions of UTI antibiotics

The time series graph of UTI antibiotic prescriptions among women ≥50 years who had received ≥2 prescriptions of methenamine hippurate in the study period before the drug shortage is presented in Figure 3, and the regression outputs are presented in Table 2. In the period before the shortage, prescriptions of UTI antibiotics fell significantly with a rate of −0.29 prescriptions per 1000 methenamine hippurate users per 14 days (95%CI −0.50, −0.08, $P=0.008$), indicating a slight pre-existing downwards trend. In the first 14-day period after the start of the drug shortage, there was a significant reduction of −7.09 prescriptions (95%CI −12.15, −2.04, $P=0.007$) followed by a significant increase of 2.41 prescriptions per 14-day period relative to the trend before the shortage (95%CI 1.39, 3.43, $P<0.001$). In the first 14-day period after reintroduction, there was a non-significant reduction of −3.29 prescriptions (95%CI −8.09, 1.51, $P=0.175$) followed by a significant reduction of −2.64 prescriptions per 14-day period compared to the trend during the shortage (95%CI −3.66, −1.63, $P<0.001$). The results show that there was a significant increase in prescribing trend of UTI antibiotics during the methenamine hippurate drug shortage, followed by a significant decrease in prescribing trend when the drug was reintroduced to the marked.

Non-equivalent control: ITSA of prescriptions of RTI antibiotics

The time series regression output of RTI antibiotic prescriptions among women ≥50 years who had received ≥2 prescriptions of methenamine hippurate in the time period before the shortage is presented in Table 2. The time series graph is presented in Supplementary data, Figure S2. Before the shortage, there was a significant downwards trend of −0.07 prescriptions per 1000 methenamine hippurate users per 14 days, which is consistent with a general slight downwards prescribing trend for RTI antibiotics (95%CI −0.13, −0.01, $P=0.016$). In the first 14-day period after the start of the shortage, there was a non-significant

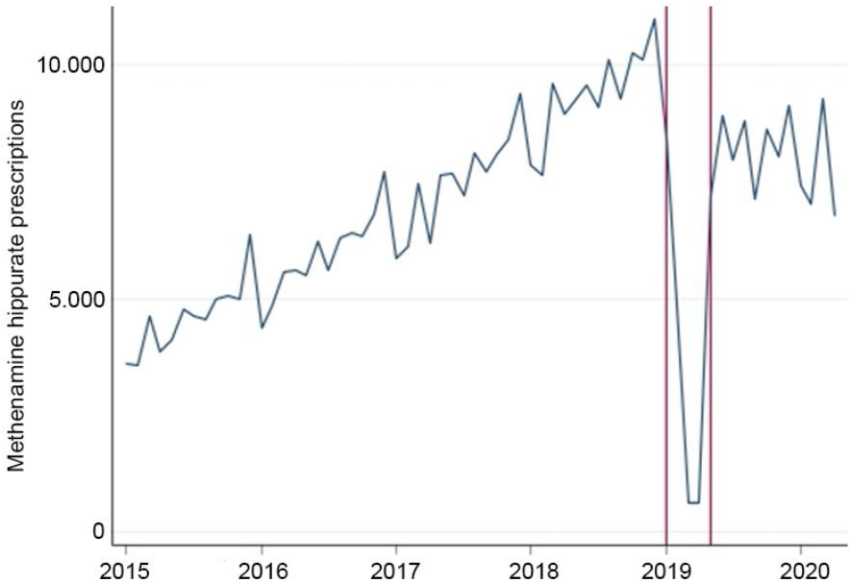

Figure 2. Number of prescriptions of methenamine hippurate per month for our study population for the period January 2015 to May 2020. The vertical lines are placed at month 1 and month 5 in 2019 illustrating the period of drug shortage. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

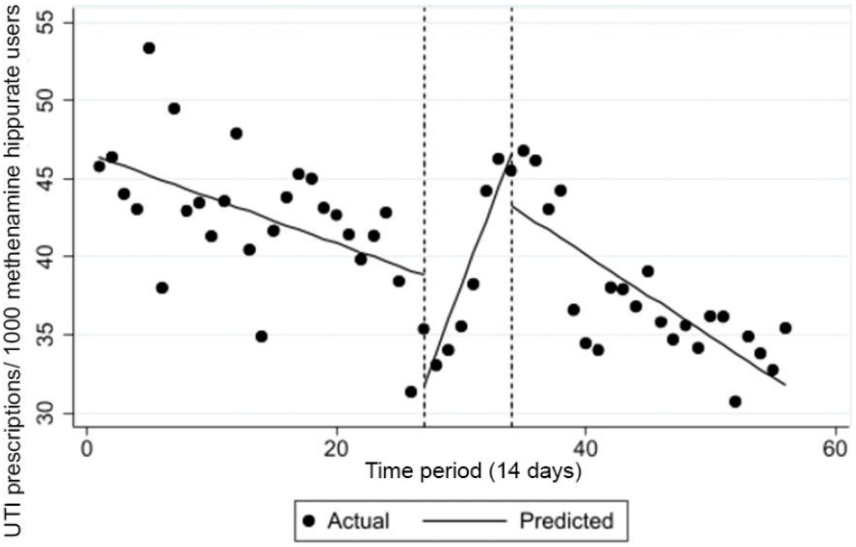

Figure 3. ITSA with two 'interventions' in time period 27 (15 January 2019–28 January 2019) and 34 (23 April 2019–6 May 2019) for prescriptions of UTI antibiotics among women ≥50 years who had received ≥2 prescriptions of methenamine hippurate in the study period before the drug shortage. The first vertical line indicates the start of the drug shortage, the second vertical line indicates the end of the shortage. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

increase of 0.16 prescriptions (95%CI −1.30, 1.61, $P=0.828$) followed by a non-significant increase of 0.10 prescriptions per 14-day period relative to the trend before the shortage (95%CI −0.16, 0.37, $P=0.426$). In the first 14-day period after reintroduction, there was a significant increase of 0.88 prescriptions (95%CI 0.08, 1.67, $P=0.032$) followed by a non-significant reduction of −0.08 prescriptions per 14-day period compared to the trend during the shortage (95%CI −0.38, 0.23, $P=0.625$). We conclude that there was no significant change in prescribing trends for RTI antibiotics during the drug shortage nor after reintroduction of methenamine hippurate.

Sensitivity analysis

For our first sensitivity analysis, we checked the impact of lowering the age limit by performing an ITSA on UTI antibiotics

Table 2. Regression output main analysis and non-equivalent control

Time series Outcome	pUTI[a] Women 50+ ≥ 2 methenamine hippurate pre-shortage (main)	pRTI[b] Women 50+ ≥ 2 methenamine hippurate pre-shortage (non-equivalent control)
Pre-shortage level	46.37	7.86
95% CI[c]	43.23, 49.52	7.11, 8.62
P	<0.001	<0.001
Pre-shortage trend	−0.29	−0.07
95% CI	−0.50, −0.08	−0.13, −0.01
P	0.008	0.016
Level shortage	−7.09	0.16
95% CI	−12.15, −2.04	−1.30, 1.61
P	0.007	0.828
Trend shortage	2.41	0.10
95% CI	1.39, 3.43	−0.16, 0.37
P	<0.001	0.426
Level reintroduction	−3.29	0.88
95% CI	−8.09, 1.51	0.08, 1.67
P	0.175	0.032
Trend reintroduction	−2.64	−0.08
95% CI	−3.66, −1.63	−0.38, 0.23
P	<0.001	0.625

[a]Antibiotic prescriptions for UTIs.
[b]Antibiotic prescriptions for RTI.
[c]Confidence interval.

for women ≥45 years who had received ≥2 prescriptions of methenamine hippurate in the study period before the shortage. This increased the study population by only 649 women from 18 345 to 18 994. The ITSA produced similar results as the main analysis with a significant increase in prescription trend for UTI antibiotics during the drug shortage, and a decrease in prescription trend after reintroduction of methenamine hippurate.

For our second sensitivity analysis, we limited the number of participants in the main analysis by also requiring ≥2 prescriptions of methenamine hippurate after the reintroduction to look at active methenamine hippurate users who continued to be active users after the shortage. In total, it was 13 658 (74.5%) women in the main study group who restarted active use after the shortage, resulting in an overall drop out of 25.5%. The age in this population was comparable to the main study population (mean age 74.7 years, SD 11.0 versus 74.6 years, SD 11.3 with median age of 75 years with an interquartile interval of 67, 83 for both groups).

We found an even dropout across all ages, albeit slightly higher in the youngest age group (50–59 years, 32%) and the two oldest age groups (90–99 years and 100–109 years, both 30%). Limiting the study population to only active users both before and after the drug shortage produced similar results as the main analysis; however, both the increase in prescribing trend during the drug shortage and the decrease in trend after the reintroduction was stronger in this population (3.25 and −3.66 prescriptions per 1000 methenamine hippurate users per time period, respectively).

For our third and fourth sensitivity analyses, we limited the number of participants in the main analysis by requiring ≥3 and ≥4 prescriptions of methenamine hippurate before the shortage (14 715 and 10 191 women, respectively). These analyses produced similar results as the main analysis. In both analyses, the increase in prescription trend during the shortage as well as the decrease after the shortage was stronger than in the main population (2.77 and −2.92 for ≥3 prescriptions, 2.64 and −2.86 for ≥4 prescriptions), however, the increase and decrease in prescription trends were larger when limiting the population to active users who continued to be active users of methenamine hippurate after the shortage in the second sensitivity analysis.

For our final sensitivity analysis, we performed the main ITSA with a wash-out period of one time period (14 days) after each time series interruption. This analysis yielded similar results as the main analysis. Regression outputs for all sensitivity analysis are provided in Table 3, the graphs are provided in the Supplementary data, Figures S3–S7.

Discussion

Main findings

The methenamine hippurate shortage in Norway in 2019 presented us with a unique opportunity—a 'natural experiment'—to explore the preventive effect of the drug by retrospectively analysing the effects of the nationwide natural withdrawal using an interrupted time series design. Our results show a significant increase in prescription trend of UTI antibiotics among female methenamine hippurate users ≥50 years during the drug shortage, followed by a significant decrease in prescription trend in the time periods after the shortage. The primary analysis results

Table 3. Regression output for the sensitivity analyses

Time series Outcome	pUTI[a] Women 45+≥2 methenamine hippurate pre-shortage	pUTI Women 50+≥2 methenamine hippurate pre-shortage and ≥2 after reintroduction	pUTI Women 50+≥2 methenamine hippurate pre-shortage + 1 wash-out period	pUTI Women 50+≥3 methenamine hippurate pre-shortage	pUTI Women 50+≥4 methenamine hippurate pre-shortage
Pre-shortage level	46.51	42.57	46.37	45.23	46.00
95% CI[b]	43.42, 49.59	39.63, 45.50	43.22, 49.53	42.23, 48.23	42.80, 49.21
P	<0.001	<0.001	<0.001	<0.001	<0.001
Pre-shortage trend	−0.29	−0.29	−0.29	−0.40	−0.40
95% CI	−0.50, −0.08	−0.48, −0.09	−0.50, −0.08	−0.60, −0.20	−0.61, −0.20
P	0.007	0.005	0.009	<0.001	<0.001
Level shortage	−6.69	−6.24	−6.68	−3.53	−1.81
95% CI	−11.75, −1.63	−10.99, −1.49	−12.58, −0.77	−8.40, 1.33	−7.18, 3.57
P	0.011	0.011	0.027	0.151	0.503
Trend shortage	2.26	3.25	2.32	2.77	2.64
95% CI	1.21, 3.30	2.26, 4.25	1.14, 3.51	1.72, 3.81	1.48, 3.80
P	<0.001	<0.001	<0.001	<0.001	<0.001
Level reintroduction	−2.82	−4.44	−3.83	−4.25	−3.71
95% CI	−7.72, 2.09	−9.72, 0.84	−8.98, 1.31	−9.61, 1.10	−9.38, 1.96
P	0.254	0.098	0.140	0.117	0.195
Trend reintroduction	−2.49	−3.66	−2.51	−2.92	−2.86
95% CI	−3.53, −1.44	−4.67, −2.66	−3.69, −1.33	−3.97, −1.88	−4.03, −1.69
P	<0.001	<0.001	<0.001	<0.001	<0.001

[a]Antibiotic prescriptions for UTIs.
[b]Confidence interval.

were reinforced by five sensitivity analyses, all of which indicated that the prescription rate of UTI antibiotics among female methenamine hippurate users ≥50 years significantly increased during the methenamine hippurate drug shortage and subsequently decreased when methenamine hippurate became available again. Surprisingly, we found a significant level change in the prescription rate of UTI antibiotics in the first 14-day period after the start of the drug shortage in our main analysis. We assumed that the drug shortage would have immediate effect only for the few participants with prescriptions close to renewal and that the number of participants running out of medication would increase throughout the shortage period. Hence, we consider the change in level in the first time period after the start of the shortage as an expression of random variation and not as a clinical effect of the shortage. This assumption is strengthened by the fact that the sensitivity analyses for participants receiving ≥3 and ≥4 prescriptions before the shortage showed no significant level change whereas both the increase in prescriptions trends during the shortage and the decrease in trend after reintroduction were stronger than in the main analysis.

We did not find significant changes in prescription trends for RTI antibiotics in the study population during the same time period, suggesting that the physician prescribing behaviour was not influenced by other changes in the health care system. We used number of prescriptions of UTI antibiotics as a measurement of number of UTIs. It seems that the lapse of the methenamine hippurate treatment coincided with increased occurrences of UTIs, whereas a reintroduction after the shortage corresponded with a decrease in UTI episodes—indicating a possible effect of the drug to reduce episodes of recurrent UTIs in women ≥50 years. To confirm these findings, a robust RCT with long-term follow up is needed.[25]

Strengths and limitations

A major strength of this study is the unique data. In Norway, methenamine hippurate is a common prescription-only drug used as preventive treatment for recurrent UTIs. Through NorPD we had access to prescription data for 18 345 active female users ≥50 years, which facilitated a robust exploration of the impact of the shortage in this population. However, our dataset also has some limitations. While NorPD register all prescriptions on dispensed medication in pharmacies, it does not contain information on drug use in nursing home facilities nor for non-prescription preventive UTI remedies such as cranberry products, ascorbic acid and D-mannose. Consequently, there are no participants from nursing homes included in this study, and we could not assess whether the use of other non-antibiotic preventive agents changed during the study period. Another aspect is participants potentially moving into nursing homes during the study period. It is possible to identify individuals where all prescriptions cease, however, we have too few prescription

variables in our dataset to draw conclusions on whether the individual had moved into a care facility or just terminated the current medication. We therefore decided to not use a stop date for all prescriptions as an exclusion criterion, potentially leaving in some participants residing in nursing homes for parts of the study period.

One major advantage of the ITSA study design is the use of pre-existing prescribing trends within the study population as the control. When appropriate, this approach effectively controls for population-based selection bias and confounding factors, minimizing the risk of time-varying confounders influencing the interpretation of the effect estimate. However, a limitation of the design is that it cannot exclude historical threats to validity such as effects from concurrent interventions or events occurring close in time to the events under study.[15] Our inclusion of a non-equivalent control time series (prescription of RTI antibiotics) suggested that there was no general change in antibiotic prescribing trend coinciding with the drug shortage. A national antibiotic stewardship intervention (RAK) started in 2016 as a result of a governmental action plan to reduce antibiotic consumption and AMR.[26,27] Even though this is a large intervention that has affected the antibiotic prescribing trend, it does not coincide timewise with the start of the methenamine hippurate drug shortage. The overall decreasing prescribing trend for antibiotics had been evident for a long time before the drug shortage and was thus not considered to affect our analysis. We reviewed all drug deficiency warnings issued in the study period and found no warning for shortage of the UTI antibiotics under study. When examining prescribing trends for the omitted antibiotics with dual indications (UTI/RTI), we did not find evidence that the changes in prescribing trends demonstrated in this study were due to a shift to more broad-spectrum antibiotics (trimethoprim/sulfamethoxazole and ciprofloxacin) or long-term preventive antibiotic treatment (trimethoprim and nitrofurantoin ≥14 DDD). However, we were not able to assess whether behavioural changes of the study population contributed to the observed change in prescribing trends of UTI antibiotics during the drug shortage and/or after reintroduction of methenamine hippurate.

Comparison with literature

Owing to the limited use of methenamine hippurate outside Scandinavia, there are few comparable register-based population studies available. To our knowledge, only one register-based case-control study exploring the long-term preventive effect of methenamine hippurate is published to date. Here, the authors found that methenamine hippurate seemed to have a preventive effect in women ≥40 with recurrent UTIs.[28] The results are in accordance with our findings. Reviews published in recent decades all report that there is insufficient evidence to conclude on the long-term preventive effect of methenamine hippurate and call for further research.[10,29–31] An important contribution to the knowledge base came with the demonstration of non-inferiority of methenamine hippurate to prophylactic antibiotics on recurrent UTIs in the ALTAR study.[7] This study was conducted on women ≥18 years in secondary health care. As the mean age of methenamine hippurate users in this study is mid-seventies, we believe it is important to also explore the effect of this drug in the older age groups.

Conclusion

During the methenamine hippurate drug shortage in 2019, we found a significant increase in prescribing trend for UTI antibiotics followed by a significant decrease in prescribing trend after reintroduction. This change in trend seems to reflect a preventive effect of methenamine hippurate on recurrent UTIs.

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Transparency declarations

No conflicts of interest to declare. Author contributions: S.H.O., U.G., H.S.B. and S.H. drafted, and P.E. revised the protocol. S.H.O. performed the analysis with U.G., H.S.B., P.E. and S.H. S.H.O. drafted the manuscript. All authors critically revised the article draft and approved the final manuscript.

Supplementary data

Figures S1 to S7 are available as Supplementary data at *JAC* Online.

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