Effect of a multifaceted antibiotic stewardship intervention to improve antibiotic prescribing for suspected urinary tract infections in frail older adults (ImpresU): pragmatic cluster randomised controlled trial in four European countries

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ABSTRACT

OBJECTIVE
To evaluate whether antibiotic prescribing for suspected urinary tract infections in frail older adults can be reduced through a multifaceted antibiotic stewardship intervention.

DESIGN
Pragmatic, parallel, cluster randomised controlled trial, with a five month baseline period and a seven month follow-up period.

SETTING
38 clusters consisting of one or more general practices (n=43) and older adult care organisations (n=43) in Poland, the Netherlands, Norway, and Sweden, from September 2019 to June 2021.

PARTICIPANTS
1041 frail older adults aged 70 or older (Poland 325, the Netherlands 233, Norway 276, Sweden 207), contributing 411 person years to the follow-up period.

INTERVENTION
Healthcare professionals received a multifaceted antibiotic stewardship intervention consisting of a decision tool for appropriate antibiotic use, supported by a toolbox with educational materials. A participatory-action-research approach was used for implementation, with sessions for education, evaluation, and local tailoring of the intervention. The control group provided care as usual.

MAIN OUTCOME MEASURES
The primary outcome was the number of antibiotic prescriptions for suspected urinary tract infections per person year. Secondary outcomes included the incidence of complications, all cause hospital referrals, all cause hospital admissions, all cause mortality within 21 days after suspected urinary tract infections, and all cause mortality.

RESULTS
The numbers of antibiotic prescriptions for suspected urinary tract infections in the follow-up period were 54 prescriptions in 202 person years (0.27 per person year) in the intervention group and 121 prescriptions in 209 person years (0.58 per person year) in the usual care group. Participants in the intervention group had a lower rate of receiving an antibiotic prescription for a suspected urinary tract infection compared with participants in the usual care group, with a rate ratio of 0.42 (95% confidence interval 0.26 to 0.68). No differences between intervention and control group were observed in the incidence of complications (<0.01 *v* 0.05 per person year), hospital referrals (<0.01 *v* 0.05), admissions to hospital (0.01 *v* 0.05), and mortality (0 *v* 0.01) within 21 days after suspected urinary tract infections, nor in all cause mortality (0.26 *v* 0.26).

CONCLUSIONS
Implementation of a multifaceted antibiotic stewardship intervention safely reduced antibiotic prescribing for suspected urinary tract infections in frail older adults.

TRIAL REGISTRATION
ClinicalTrials.gov NCT03970356.

WHAT IS ALREADY KNOWN ON THIS TOPIC
Decisions on antibiotic prescribing for urinary tract infections in frail older adults are challenging and often lead to inappropriate antibiotic use, contributing to the development of antibiotic resistance

Guidelines promote restrictive antibiotic use; however, implementation in practice is difficult owing to the complexity of antibiotic prescribing decisions and the heterogeneity within the older adult care setting

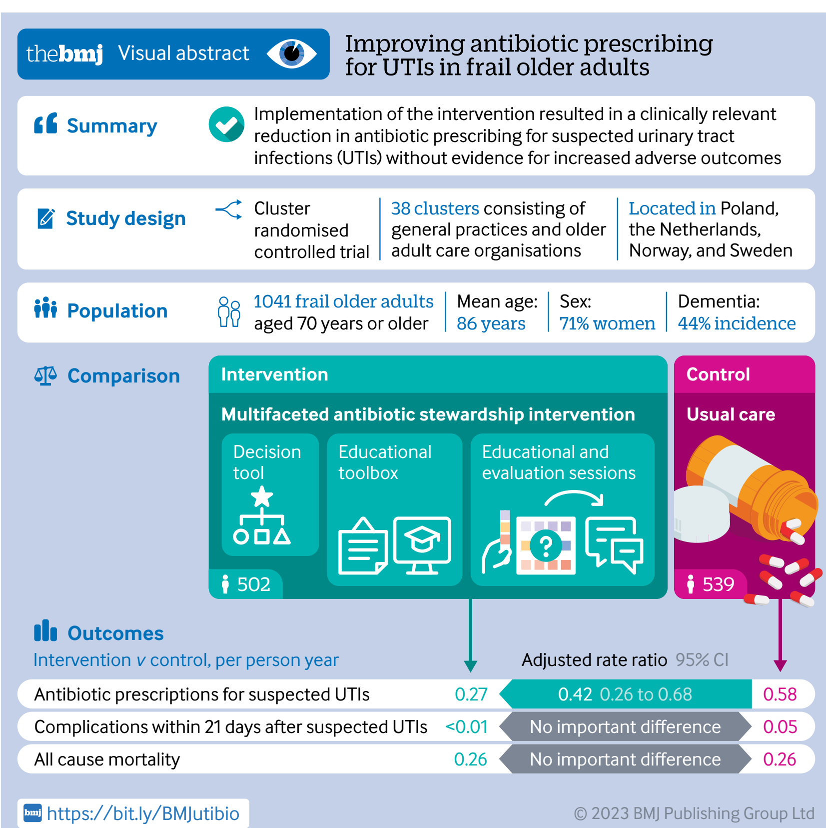
WHAT THIS STUDY ADDS
Implementation of a multifaceted antibiotic stewardship intervention using a modified participatory-action-research approach across diverse older adult care settings in Poland, the Netherlands, Norway, and Sweden resulted in a clinically relevant reduction in antibiotic prescribing for suspected urinary tract infections without an increase in complication rates

Introduction
Antibiotic resistance is a major threat to global health.[1] Inappropriate antibiotic use is an important contributor to antibiotic resistance.[2] Frequently, frail older adults inappropriately receive antibiotics for a suspected urinary tract infection for non-specific symptoms, such as a mental status change or smelly urine.[3 4] In recent years, consensus has been reached that non-specific symptoms are not directly attributable to urinary tract infections and do not require antibiotic treatment.[5 6] Furthermore, although the prevalence of asymptomatic bacteriuria is high in frail older adults, positive urine

test results are often misinterpreted as proof of a urinary tract infection.[5 7] To increase appropriate antibiotic use, current guidance is to be restrictive with antibiotic prescribing when symptoms specific to the urinary tract are absent.[8-11] Implementation in practice is, however, challenging because of the complexity of antibiotic prescribing decisions by general practitioners in older adult care settings.[12 13]

To date, multiple studies have evaluated antibiotic stewardship interventions in older adult care settings. While many show promising effects on reducing antibiotic use, the level of evidence is still limited because few studies use a randomised design.[14-18] Moreover, the applicability across different countries is uncertain owing to great variability in antibiotic use and heterogeneity in organisation of care between and within countries.[19 20] This dearth of evidence indicates a need to evaluate an antibiotic stewardship intervention across the heterogeneous older adult care setting in multiple countries. Effective implementation might be possible through participatory action research, a method in which healthcare professionals are actively engaged and tailor the intervention to their own situation.[21]

We developed a multifaceted antibiotic stewardship intervention, including a decision tool for appropriate antibiotic prescribing for urinary tract infections that was previously developed by an international expert team.[5] A previous qualitative study guided the development and tailoring of the antibiotic stewardship intervention.[22] In the current study, we evaluated whether this multifaceted antibiotic stewardship intervention, implemented using a participatory-action-research approach,[23] was effective in reducing antibiotic prescribing for suspected urinary tract infections in various older adult care settings in Poland, the Netherlands, Norway, and Sweden, compared with usual care.



Methods

We conducted a pragmatic cluster randomised controlled trial in general practices and older adult care organisations in Poland, the Netherlands, Norway, and Sweden, in which we compared the effectiveness of a multifaceted antibiotic stewardship intervention with usual care. A detailed protocol of the improving antibiotic prescribing for urinary tract infections in frail older adults (ImpresU) study was previously published.[23] We followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines for cluster randomised trials.[24]

Clusters and setting

A cluster (the unit of randomisation) consisted of one or more general practices and older adult care organisations, together providing care for at least 20 older adults. Nursing homes were included in Poland, Norway, and Sweden, and residential care homes and home care organisations were included in the Netherlands. Medical care was provided by general practitioners; except in Norway, where nursing homes themselves employ doctors who often have a background in general practice or geriatrics. Recruitment of clusters was performed through the networks of the research groups in each country.

Participants

For inclusion, participants had to be 70 years or older, have physical or mental disabilities, or both, and dependency in activities of daily living, not use prophylactic antibiotics, not receive hospice care, and not be estimated to have a very limited life expectancy (≤1 month). Participation ended when participants died, moved away from the cluster, started prophylactic antibiotics, received hospice care, or were estimated to have a very limited life expectancy (≤1 month). Participants were excluded from analysis if they participated for less than two months. At study start, the care organisations identified eligible participants and provided written study information. Enrolment was continued during the study for new patients in the care of the participating care organisations. A researcher or nurse obtained written informed consent from participants (or their representatives in case of legal incapacity).

Randomisation and blinding

In November 2019, an independent data manager performed block randomisation to assign clusters to intervention or usual care using SAS software (version 9.4; SAS Institute), stratified by country and cluster size (small ≤7%, medium 8-14%, large ≥15% of participants, see supplementary table S1). Owing to the nature of the intervention, blinding was not possible. To minimise the risk of contamination, the study aims were not explicitly stated to the control clusters; we invited them to participate in research on urinary tract infections in which they would be randomised to receive education either during the study or after study completion.

Intervention

The healthcare professionals in the intervention clusters received a multifaceted antibiotic stewardship intervention. Its development and tailoring were guided by our previous qualitative interview study; details on the design have been published previously.[22 23] We report the intervention following the Template for Intervention Description and Replication (TIDieR) guidelines.[25] The control clusters provided care as usual.

The intervention period was intended to last four months and began in February 2020. After a month, it was interrupted by the first wave of the covid-19 pandemic, resulting in a six month pause. In September 2020, the intervention period was resumed after a feasibility assessment of restarting the trial and intervention, considering the burden of the pandemic in clinical practice. It was restarted for two more months in Poland and the Netherlands (September to October 2020), and three more months in Norway and Sweden (September to November 2020).

Intervention design

Figure 1 provides a visual overview of the intervention. The antibiotic stewardship intervention consisted of a decision tool to guide appropriate antibiotic use for suspected urinary tract infections in frail older adults, which was developed by an international expert team and is congruent with the latest treatment guidelines.[5 8-11] To support implementation, we composed a toolbox of educational materials, such as pocket cards, posters, and information leaflets. These materials targeted healthcare professionals as well as patients and informal caregivers. Supplementary material S1 includes the decision tool and examples of toolbox materials.[23]

We used a participatory-action-research approach for implementation, integrated in sessions for education and evaluation. In participatory action research, action researchers go through a cyclical process of reflection on the local situation, development and planning of interventions, and the action of implementation, followed by returning to reflection.[26 27] We modified this approach through previous development of the decision tool and toolbox and providing education on its use.[22]

Intervention in practice

At the start of the intervention period, healthcare professionals received information about the decision tool and toolbox materials. In each cluster, one or more educational sessions were held with general practitioners and nursing staff, with a median duration of 60 minutes (range 40-120). During the educational sessions, attending healthcare professionals (median 5, range 1-21) received training from the researchers on how to recognise urinary tract infections using the decision tool, followed by joint reflection on local practice and plans for implementation. If the session had taken place before the covid-19 pause, a refresher session was held on restart of the intervention period. Additionally, in 17 of 19 intervention clusters, at least one evaluation session took place with a median duration of 30 minutes (range 30-60). In these sessions, healthcare professionals (median 3, range 1-16) and researchers reflected on the implementation process and planned additional actions. When possible, sessions were held at the workplace of the healthcare professionals; however, most took place online because of the covid-19 pandemic. Researchers and healthcare professionals had regular phone contact to monitor implementation progress. In one general practice and one residential care home (part of two separate Dutch clusters), no sessions took place as these facilities no longer wished to participate in the intervention after the covid-19 pause.

The antibiotic stewardship intervention and its implementation were tailored in each country by the

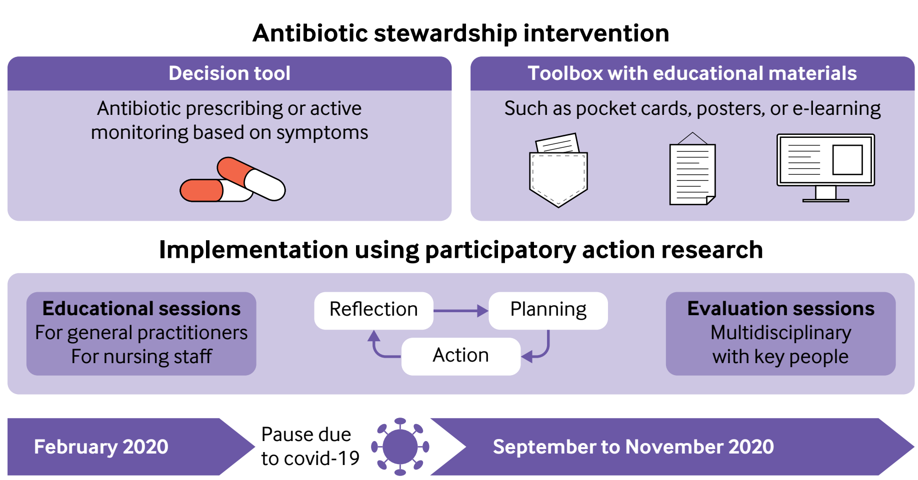
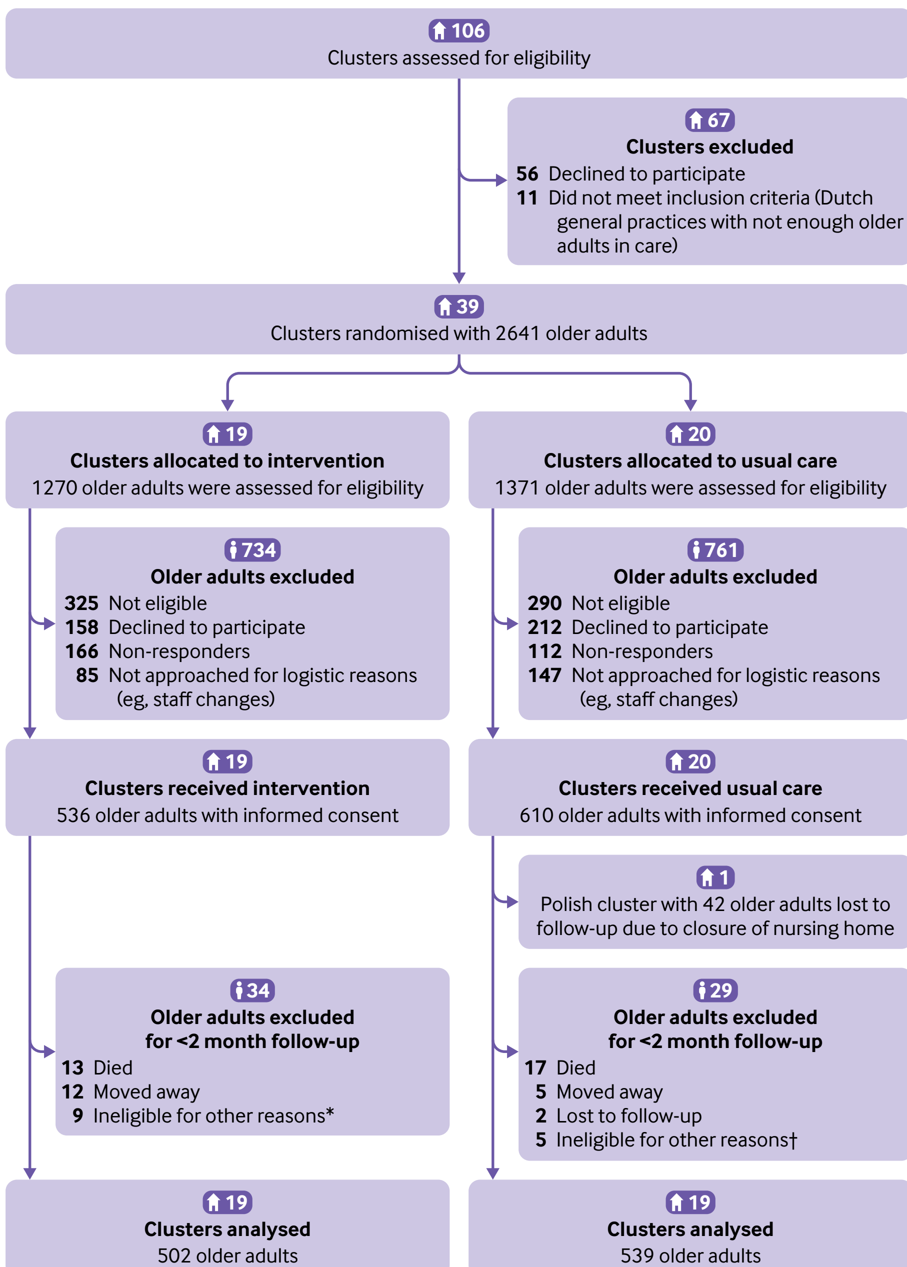


Fig 1 | Design and implementation of the antibiotic stewardship intervention

research teams based on their local experience and qualitative interviews, and within the clusters by the healthcare professionals through the participatory-action-research approach. We aligned toolbox materials with national guidelines and added locally available materials. The qualitative study showed knowledge gaps on recognition of symptoms related to urinary tract infection and asymptomatic bacteriuria, which we covered during the educational sessions.[22] Additionally, interview quotes were used in these sessions to elicit discussion on local attitudes, communication, and organisation of care—for example, we reflected on participants' personal role and the role of others when a urinary tract infection was suspected.[22] To accommodate varying group sizes and differences in local collaborations, the educational sessions were multidisciplinary in Norway and Poland but separate for general practitioners and nursing staff in Sweden and the Netherlands. Across clusters, specific efforts by action researchers (ie, healthcare professionals and researchers) varied. For example, action researchers worked with other stakeholders besides doctors and nursing staff (eg, healthcare helpers, general practice assistants, or managers), held additional sessions internally or with researchers, and edited toolbox materials. We will



* 5 used prophylactic antiobiotics, 1 had very limited life expectancy, 3 withdrew consent
† 1 used prophylactic antiobiotics, 3 had very limited life expectancy, 1 in hospice care

Fig 2 | Flow diagram of clusters and participants through the trial. The final analysis included 1041 participants in 38 clusters consisting of 43 general practices and 43 older adult care organisations

Table 1 | Baseline characteristics of participants in clusters assigned to a multifaceted antibiotic stewardship intervention or usual care (control)

Characteristics	Antibiotic stewardship intervention (n=502)	Usual care (n=539)	Total* (n=1041)
Country:			
Norway	128 (25)	148 (27)	276 (26.5)
Poland	150 (30)	175 (32)	325 (31.2)
Sweden	101 (20)	106 (20)	207 (19.9)
The Netherlands	123 (25)	110 (20)	233 (22.4)
Mean (SD) age (years)	86.4 (7.3)	86.2 (7.7)	86.3 (7.5)
Women	347 (69)	391 (73)	738 (70.9)
Site of residence:			
Nursing home	379 (75)	429 (80)	808 (77.6)
Residential care home	88 (18)	110 (20)	198 (19.0)
Home care	35 (7)	0	35 (3.4)
Comorbidity:			
Cardiovascular disease	345 (69)	375 (70)	720 (69.2)
Pulmonary disease	77 (15)	113 (21)	190 (18.3)
Diabetes mellitus	84 (17)	103 (19)	187 (18.0)
Immunosuppression	26 (5)	13 (2)	39 (3.8)
Disorders of kidney/urinary tract	121 (24)	105 (19)	226 (21.7)
Dementia	189 (38)	273 (51)	462 (44.4)
Mild cognitive impairment†	152 (30)	125 (23)	277 (26.6)
Recurrent urinary tract infections (≥3 yearly)	63 (13)	67 (12)	130 (12.5)
Indwelling urinary catheter	35 (7)	43 (8)	78 (7.5)
Urinary incontinence	278 (55)	324 (60)	602 (57.8)
Faecal incontinence	139 (28)	143 (27)	282 (27.1)
Mean (SD) Katz ADL score‡	2.6 (2.0)	2.9 (2.0)	2.8 (2.0)

ADL=activities of daily living; SD=standard deviation.
*No missing data on country, age, sex, site of residence. For other variables, <2% was registered as missing/unknown, with the exception of recurrent urinary tract infections (n=30, 2.9%).
†Pragmatically defined as cognitive impairment without dementia diagnosis.
‡Range 0-6 from independent to dependent.

evaluate the implementation separately in a process evaluation.[23]

Outcomes

The primary outcome measure was the number of antibiotic prescriptions for suspected urinary tract infections. The clinical suspicion of a urinary tract infection was not defined, but rather left to the attending doctor. Prescriptions were registered on the day of a suspected urinary tract infection or during 21 days of follow-up to include prescriptions after a wait-and-see policy. Secondary outcomes included the number of antibiotic prescriptions during office hours on the day of a suspected urinary tract infection (we had planned in the protocol to evaluate this within the 21 days; however, data on whether the prescription was within or outside of office hours were only available on the day the urinary tract infection was suspected and not on days 2 to 21), the number of inappropriate (not adherent to the decision tool) antibiotic prescriptions for suspected urinary tract infections, and the number of suspected urinary tract infections. Additional secondary outcomes were adverse outcomes: the number of complications within 21 days after each suspected urinary tract infection (ie, the presence (yes or no) of delirium, pyelonephritis, sepsis, or renal failure), the number of all cause hospital referrals within 21 days after each suspected urinary tract infection, the number of all cause hospital admissions within 21 days after each suspected urinary tract infection, all cause mortality within 21 days after each suspected urinary tract infection, and all cause mortality. All outcomes were assessed at participant level and expressed per person year.

Several protocol amendments were made at the beginning of the study. We added the outcome on antibiotic prescriptions in office hours, specified hospital referral and admission to be all cause instead of related to urinary tract infection because all cause is more objective and easier to measure, and further specified mortality as two secondary outcomes (all cause mortality within 21 days after suspected urinary tract infections and all cause mortality).

Procedures

Data collection took place during a five month baseline period (September 2019 to January 2020) and a seven month follow-up period (Poland and the Netherlands November 2020 to May 2021, Norway and Sweden December 2020 to June 2021). The general practitioner, nurse, or researcher prospectively completed case report forms on paper based on information from a healthcare professional or medical file, and researchers subsequently registered these electronically in a secure online database. Baseline characteristics for each participant were registered at inclusion. When a urinary tract infection was suspected, clinical details, antibiotic treatment, and disease course were prospectively registered on the day of consultation and after seven and 21 days of follow-up (primary and secondary outcomes except all cause mortality). To avoid missing suspected urinary tract infections with antibiotic prescriptions (eg, if forgotten, prescribed out of hours, or during a hospital stay), we retrospectively registered these through a review of the medical files in Poland, the Netherlands, and Norway, and monthly consultation of attending healthcare professionals in Sweden. All cause mortality (secondary outcome) was registered when patients stopped study participation. For scoring the appropriateness of antibiotic prescriptions (secondary outcome), an independent researcher blinded to the trial arms scored prescriptions as appropriate, inappropriate, or unknown when information was missing based on the decision tool (see supplementary material S2).

Covid-19 impact

We paused the study from March until August 2020, during the intervention period. During the follow-up period, we collected anonymised data on covid-19 incidence in the participating care organisations at the cluster level only.

Sample size

For the sample size calculation, we assumed a clinically relevant reduction in antibiotic prescribing rates from 0.75 to 0.40 per person year, an intracluster correlation coefficient of 0.06, one sided testing, an α of 0.05, a power of 0.8, and a cluster size of 10 patients contributing for seven months in the follow-up period.[23 28 29] Using a Wilcoxon test with an adjustment for cluster randomisation, it was estimated that 333 patients would be needed. To account for

Table 2 | Primary and secondary outcomes

		Antibiotic stewardship intervention*		Usual care†		Rate ratio (95% CI)‡					
						Primary analyses				Multiple imputation analyses	
	Period	No	Per person year	No	Per person year	Unadjusted	P value	Adjusted§	P value	Adjusted§	P value
Primary outcome											
Antibiotic prescriptions for suspected UTIs	Baseline	87	0.50	77	0.44	0.41 (0.25 to 0.65)	<0.001	0.42 (0.26 to 0.68)	<0.001	0.39 (0.24 to 0.63)	<0.001
	Follow-up	54	0.27	121	0.58						
Secondary outcomes											
Antibiotic prescriptions in office hours on day of suspected UTI	Baseline	76	0.44	46	0.26	0.31 (0.18 to 0.55)	<0.001	0.33 (0.19 to 0.57)	<0.001	0.30 (0.17 to 0.53)	<0.001
	Follow-up	38	0.19	75	0.36						
Inappropriate antibiotic prescriptions for suspected UTIs¶	Baseline	28	0.16	22	0.13	0.44 (0.18 to 1.07)	0.07	0.47 (0.20 to 1.13)	0.09	0.44 (0.18 to 1.04)	0.06
	Follow-up	23	0.11	41	0.20						
Suspected UTIs	Baseline	98	0.56	107	0.62	0.49 (0.33 to 0.75)	0.001	0.51 (0.34 to 0.77)	0.002	0.48 (0.32 to 0.73)	0.001
	Follow-up	65	0.32	150	0.72						
Complications within 21 days after suspected UTI**	Baseline	7	0.04	10	0.06	—	—	—	—	—	—
	Follow-up	1	<0.01	10	0.05						
All cause hospital referrals within 21 days after suspected UTI	Baseline	0	0	0	0	—	—	—	—	—	—
	Follow-up	1	<0.01	3	0.01						
All cause hospital admissions within 21 days after suspected UTI	Baseline	2	0.012	5	0.03	—	—	—	—	—	—
	Follow-up	2	0.01	10	0.05						
Mortality within 21 days after suspected UTI	Baseline	3	0.02	0	0	—	—	—	—	—	—
	Follow-up	0	0	3	0.01						
All cause mortality	Baseline	21	0.12	26	0.15	1.24 (0.60 to 2.57)	0.55	1.03 (0.48 to 2.21)	0.93	1.08 (0.51 to 2.31)	0.84
	Follow-up	52	0.26	55	0.26						

CI=confidence interval; UTI=urinary tract infection.
*19 clusters, 502 participants. Baseline: 174 person years. Follow-up: 202 person years.
†19 clusters, 539 participants. Baseline: 174 person years. Follow-up: 209 person years.
‡Odds ratios are provided for all cause mortality.
§Adjusted for age, sex, activities of daily living dependency, presence of catheter, dementia, recurrent UTIs, diabetes, and kidney disorders. All cause mortality is additionally adjusted for presence of cardiovascular disease and immunosuppression.
¶Inappropriate according to the decision tool.
**Presence of delirium, pyelonephritis, sepsis, or renal failure.

Subgroup	Antibiotic prescription rate per person year: Intervention Baseline	Intervention Follow-up	Usual care Baseline	Usual care Follow-up	Adjusted rate ratio (95% CI)
All patients	0.50	0.27	0.44	0.58	0.42 (0.26 to 0.68)
Poland	0.30	0.14	0.43	0.68	0.28 (0.11 to 0.73)
The Netherlands	0.87	0.24	0.68	0.58	0.32 (0.12 to 0.82)
Norway	0.48	0.35	0.31	0.68	0.40 (0.16 to 1.03)
Sweden	0.37	0.42	0.39	0.23	2.25 (0.57 to 8.88)
Women	0.57	0.30	0.43	0.58	0.43 (0.25 to 0.73)
Men	0.36	0.18	0.47	0.58	0.40 (0.15 to 1.06)
Patients with dementia	0.70	0.37	0.38	0.64	0.33 (0.17 to 0.64)
Patients without dementia	0.39	0.22	0.53	0.53	0.56 (0.28 to 1.12)
Patients with urinary incontinence	0.51	0.38	0.43	0.60	0.53 (0.29 to 0.96)
Patients without urinary incontinence	0.48	0.15	0.47	0.56	0.24 (0.11 to 0.54)
Patients with catheter	1.31	0.60	1.07	1.22	0.37 (0.11 to 1.21)
Patients without catheter	0.44	0.25	0.38	0.54	0.43 (0.26 to 0.74)
Patients aged <80	0.37	0.24	0.41	0.64	0.38 (0.14 to 1.08)
Patients aged ≥80	0.54	0.28	0.45	0.56	0.44 (0.26 to 0.75)

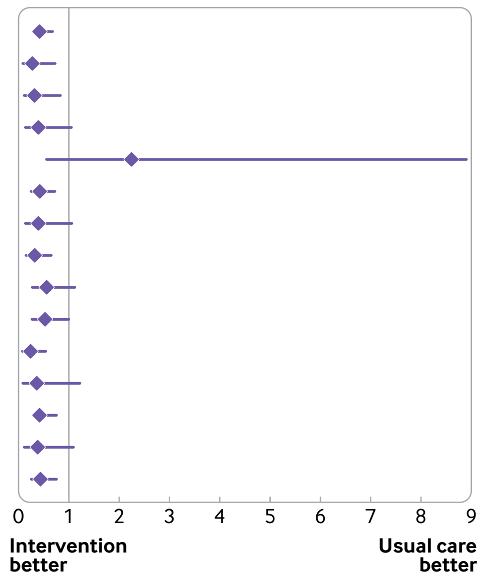


Fig 3 | Effect of the antibiotic stewardship intervention on the primary outcome (number of antibiotic prescriptions for suspected urinary tract infections per person year) across subgroups per country, in men, women, patients with and without dementia, with and without urinary incontinence, with and without an indwelling catheter, and younger and older than 80 years. CI=confidence interval

loss to follow-up, we increased the cluster size to 20 patients. In total, we aimed to include 680 participants in 34 clusters.[23]

Data analysis

For the primary outcome, we used a generalised linear mixed model for count outcomes with a negative binomial distribution. Two separate random intercepts were included to correct for clustering at the level of a cluster (general practice and corresponding care organisation) and to correct for repeated measurements within patients. The comparison between intervention and control group was estimated with the time by treatment interaction (period by intervention). In a second model, we adjusted for prespecified prognostic factors: age, sex, dependency in activities of daily living (Katz activities of daily living score),[30] presence of an indwelling catheter, dementia, recurrent urinary tract infections, diabetes mellitus, and kidney disorders. For secondary analyses on the numbers of suspected urinary tract infections, antibiotic prescriptions in office hours, and inappropriate antibiotic prescriptions, we used the generalised linear mixed model for negative binomial distributions as described above. Because of the low incidence, we only present descriptive statistics for the number of complications, hospital referrals, hospital admissions, and mortality registered within 21 days after each suspected urinary tract infection. For all cause mortality, we used a generalised linear mixed model for binary outcomes, with a random intercept to correct for clustering at the cluster level. In the second model we adjusted for two additional prespecified prognostic factors: cardiovascular disease and immunosuppression. All analyses were performed according to the intention-to-treat principle.

Subsequently, we performed planned subgroup analyses to assess the primary outcome in groups in each country, with different sex, age younger or older than 80 years, and the presence of dementia, urinary incontinence, and an indwelling catheter. We assessed whether effect modification was present by incorporating interaction terms in the adjusted model described above. This model was compared with the adjusted model using a likelihood ratio test.

In sensitivity analyses, we performed multiple imputation to assess the impact of missing values on variables selected as potential confounders. We imputed missing data using chained equations with predictive mean matching for continuous variables and regression models for dichotomous and count variables, and included corrections for clustering. The imputation model was performed stratified per trial arm and included the prognostic factors specified previously, urinary incontinence, faecal incontinence, mild cognitive impairment, pulmonary disease, country, site of residence, and study period.[31] We generated 40 imputed datasets. The primary and secondary analyses were repeated as described above, and the results were pooled using Rubin's rules.[32]

To evaluate whether the covid-19 pandemic affected intervention and usual care clusters differently, we assessed the presence of covid-19 outbreaks in participating clusters in anonymised data. We defined an outbreak as three or more older adults with a positive SARS-CoV-2 test result registered in the same month in the same care organisation, and we present descriptive statistics.

Data were analysed with SPSS version 26 (descriptive statistics) and Stata version 14 (mixed model analyses). Multiple imputation was performed with the mice package 3.13 in R version 4.03.

Patient and public involvement

The design of the antibiotic stewardship intervention was informed by results from qualitative in-depth interviews with patients, informal caregivers, and healthcare professionals in the four participating countries.[23] In the process of the trial design, a meeting was held with representatives of Network Utrecht care for the elderly (NUZO), Julius Center, University Medical Center Utrecht, the Netherlands. Their suggestions on the protocol were taken into account—for example, we included delirium among the registered complications and created patient directed toolbox materials. Also, the project was discussed with healthcare professionals in a workgroup meeting of the Academic Network Medicine for Older People (UNO), Amsterdam UMC, the Netherlands.

Results

Participants were recruited from June 2019 to June 2021 in 39 participating clusters. In total, 1146 older adults provided signed informed consent. In the usual care group, one Polish cluster with 42 older adults withdrew from the study in December 2019 (the baseline period) because the nursing home closed and the data could not be retrieved. In addition, 63 participants were excluded because they participated for less than two months. In total, we included 1041 participants in 38 clusters consisting of 43 general practices and 43 older adult care organisations in the analysis. Of these, 19 clusters with 502 participants were in the intervention group and 19 clusters with 539 participants were in the usual care group. Figure 2 shows the flow of clusters and participants in the trial.

Baseline characteristics of participants were generally balanced between the trial arms (table 1). The majority (70.9%) of participants were women and the mean age was 86.3 years (standard deviation 7.5). Many participants had comorbidities, most frequently cardiovascular disease (69.2%). The presence of dementia was less frequent in the intervention group (38%) compared with the usual care group (51%). Participant characteristics showed some variation between countries (see supplementary table S2). In the Netherlands, participants received care in a residential care home or from a home care organisation. The three clusters with participating home care organisations were randomised to the intervention group. In Poland, Norway, and Sweden, only nursing home residents were included. Polish participants were younger on average (mean 83 years). The percentage of participants with dementia was highest in Norway (68%) and lowest in Sweden (24%). In 62% of urinary tract infection episodes in the follow-up period, at least one symptom specific to the urinary tract was reported, of which the most common was urgency/frequency of urination (49%) (see supplementary table S3). Fever was reported in 18% of urinary tract infection episodes, more frequently in the usual care group than in the intervention group (21% *v* 11%).

Primary and secondary outcomes

Of 1041 participants, 799 were not prescribed antibiotics for a suspected urinary tract infection, and 242 participants received on average 1.4 (range 1-5) antibiotic prescriptions during the entire study period. In the baseline period, the number of antibiotic prescriptions for suspected urinary tract infections was 87 per 174 person years (0.50 per person year) in the intervention group and 77 per 174 person years (0.44 per person year) in the usual care group (table 2). The primary outcome in the follow-up period was 54 per 202 person years (0.27 per person year) in the intervention group and 121 per 209 person years (0.58 per person year) in the usual care group. Supplementary material S3 displays the number of antibiotic prescriptions per month in the follow-up period. The unadjusted analysis showed that participants in the intervention clusters in the follow-up period had a lower rate of receiving an antibiotic prescription for a suspected urinary tract infection compared with participants in control clusters, with a rate ratio of 0.41 (95% confidence interval 0.25 to 0.65). When adjusted for potential confounders, the rate ratio was 0.42 (0.26 to 0.68). A similar rate ratio of 0.39 (0.24 to 0.63) resulted from the multiple imputation analysis (table 2).

In the adjusted models for secondary outcomes, the intervention group had a lower rate of antibiotic prescriptions on index consultation in office hours (0.33, 95% confidence interval 0.19 to 0.57), a lower rate of inappropriate antibiotic prescriptions (0.47, 0.20 to 1.13), and a lower rate of suspected urinary tract infections (rate ratio 0.51, 0.34 to 0.77) compared with the usual care group (table 2). The incidence rates of complications (<0.01 *v* 0.05 per person year), hospital referrals (<0.01 *v* 0.05), hospital admissions (0.01 *v* 0.05), and mortality (0 *v* 0.01) within 21 days after suspected urinary tract infections were lower in the intervention group; owing to the low numbers, we only provide descriptive statistics. All cause mortality was similar between groups; with 52 deaths (0.26 per person year) in the intervention group and 55 deaths (0.26 per person year) in the usual care group, participants in the intervention group had an adjusted odds of mortality of 1.03 (0.48 to 2.21). Multiple imputation analyses provided similar results (table 2).

Subgroup analyses

The effect of the intervention on the primary outcome appeared stable across subgroups of men versus women, with and without an indwelling catheter, and in patients younger and older than 80 years (fig 3, supplementary table S4). The intervention effect was stronger in patients with dementia (rate ratio

0.33, 95% confidence interval 0.17 to 0.64) compared with patients without dementia (0.56, 0.28 to 1.12), and in patients without urinary incontinence (0.24, 0.11 to 0.54) compared with patients with urinary incontinence (0.53, 0.29 to 0.96). When comparing subgroups in each country, the intervention effect was similar in Poland (0.28, 0.11 to 0.73), the Netherlands (0.32, 0.12 to 0.82), and Norway (0.40, 0.16 to 1.03), but not in Sweden (2.25, 0.57 to 8.88).

Covid-19 outbreaks

In the follow-up period, 15 of 38 participating clusters had at least one covid-19 outbreak (see supplementary table S5). Generally, the presence of outbreaks appeared to be relatively balanced between intervention and control clusters; however, differences between countries were large. While seven out of eight clusters in Poland had outbreaks, in Norway, no clusters had outbreaks. In the Netherlands, three intervention and two control clusters (out of 11) had outbreaks. In Sweden, outbreaks occurred in three intervention clusters only (see supplementary table S5).

Discussion

In this pragmatic cluster randomised controlled trial in older adult care settings in four European countries, implementation of a multifaceted antibiotic stewardship intervention resulted in a substantial, clinically relevant reduction in antibiotic prescription rates for suspected urinary tract infections with a rate ratio of 0.42. This reduction in antibiotic use appeared to be safe, as adverse outcomes and all cause mortality did not differ between groups.

Strengths and weaknesses of this study

The strength of this study lies in the combination of methodologies that allowed us to deal with the complexity of this topic. The previous qualitative study gave us a deeper understanding of the relevant decision making processes, the knowledge gaps in recognition of asymptomatic bacteriuria and urinary tract infections, and the heterogeneous care settings, thereby improving the antibiotic stewardship intervention.[22] The participatory-action-research component enabled healthcare professionals to tailor implementation to their practice. Finally, the pragmatic controlled trial design in a diverse international setting increased generalisability of the results.

This study also had several limitations. Firstly, we prospectively registered data on suspected urinary tract infections and thus could not collect information on antibiotic prescriptions for other indications. Theoretically, the decrease in antibiotic use for suspected urinary tract infections could have been accompanied by an increase in antibiotic use for other indications.[33] This could be why a smaller number of patients in the intervention group presented with fever compared with the usual care group (see supplementary table S3). Our intervention could therefore have prompted healthcare professionals to better evaluate symptoms in patients with fever. Secondly, although we do not observe an evident increase in the number of prescriptions in intervention clusters during the seven month follow-up period (see supplementary material S3), we did not evaluate long term sustainability of our results. Additionally, it would have been valuable to evaluate patient reported outcomes, microbiological outcomes, and the cost effectiveness of our results. We chose not to evaluate these outcomes to minimise participant burden and increase study feasibility. Furthermore, we used one sided testing for our power calculation; nevertheless, we included enough participants and reported our results in line with recommendations.[34] Finally, a possible limitation is that the covid-19 pandemic affected the study. During the pandemic, lower antibiotic use has been reported in general practice; however, this decrease was found predominantly for respiratory tract infections, not urinary tract infections.[35 36] Any negative impact on the validity and generalisability of our results is likely to be limited, because the intervention and control groups were similarly affected by covid-19 outbreaks in the countries where the intervention was effective (except for Sweden). That the intervention was effective despite difficult circumstances for implementation is promising.

Our study yielded several unanticipated findings. Firstly, clusters receiving usual care showed an overall increase in antibiotic prescribing over time (table 2). Prospectively registering urinary tract infections might have prompted awareness of prescribing behaviour (ie, a Hawthorne effect) and consequently lowered prescription rates in the baseline period in both groups.[37] The overall increase in the follow-up period could reflect regression to the mean in clusters with usual care. Secondly, in Sweden, no apparent beneficial intervention effect was observed. Importantly, the rate ratio estimate of 2.25 (95% confidence interval 0.57 to 8.88) has considerable uncertainty (fig 3). The antibiotic prescribing rates were relatively low in both the intervention group and the usual care group and decreased even further in the usual care group. These low rates are presumably a consequence of the Swedish strategic programme against antibiotic resistance (Strama), which has been implemented for many years and includes specific actions for urinary tract infections in older adults.[38 39] Furthermore, patients with dementia were under-represented in Sweden (see supplementary table S2), whereas the intervention effect appeared to be much stronger in this subgroup.

Comparison with literature

Our findings are consistent with several previous studies in showing a reduction in antibiotic use for suspected urinary tract infections without evidence for increased adverse outcomes.[14-18 40 41] Our intervention was centred around a decision tool and, similar to others, was multifaceted with an educational component.[14 42 43] In the United States, a comparable decision tool restricted to uncomplicated cystitis was developed and evaluated as useful in long term care settings.[41 44] Our results in European settings further endorse consensus recommendations for use of a decision tool.[6] When a meta-analysis evaluated the impact of antibiotic stewardship interventions in long term care settings, it found that they were associated with a 14% reduction in antibiotic use.[18] Although study designs varied considerably, our effect size—a rate ratio of 0.42—is larger compared with most studies. This is exactly the same effect size as found in a recent Danish cluster randomised trial.[40] Key shared factors for success might have been the active participation of nursing staff and incorporation of reflection to deal with behavioural aspects of decision making.[40] In our study, we included this behavioural component through a participatory-action-research approach. This approach is still uncommon but could have potential in antibiotic stewardship, given the complexity of the setting comprising multiple stakeholders.[21 25 45-48] Understanding the value of the separate components of multifaceted interventions remains difficult. In a recent review, all included studies reported positive effects on (appropriate) antibiotic use; however, the authors underlined that compliance with components was poorly reported.[49] To improve reporting, the TIDieR checklist can provide guidance.[25] We used this checklist and plan to identify factors for successful implementation in a separate process evaluation.[23]

Implications for practice and future research

Our multifaceted antibiotic stewardship intervention can be recommended for use in clinical practice to reduce antibiotic use for suspected urinary tract infections in frail older adults. From our subgroup analyses, the antibiotic stewardship intervention appears to be effective across most subgroups, indicating wide applicability for implementation. The effectivity across diverse settings in our study makes it plausible that tailored implementation in other countries would be effective as well. Moreover, we find it promising that the intervention effect appeared to be much stronger in patients with dementia, because antibiotic stewardship usually is difficult in this population.[50] Therefore, implementation should perhaps be prioritised in care settings for patients with dementia. Another relevant finding is that the intervention effect appeared to be weaker in patients with urinary incontinence. The decision tool might be difficult to apply because recognition of symptoms specific to the urinary tract is more complicated in patients with incontinence.[22] It might be valuable to develop tools for better recognition of symptoms of urinary tract infections in these patients. Finally, whereas our study focused on reducing antibiotic use through improving recognition of urinary tract infections, parallel work is needed to improve prevention of urinary tract infections, optimise choice and duration of antibiotic treatment, and reduce unnecessary prophylactic antibiotic use.[51]

Conclusion

A multifaceted antibiotic stewardship intervention safely reduced antibiotic prescribing for suspected urinary tract infections in older adults. Implementation across diverse older adult care settings requires the active participation of all healthcare professionals, as well as tailoring to the local situation.

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Data sharing: Relevant anonymised data will be made available upon reasonable request.

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The study results will be communicated to study participants that indicated their interest. Furthermore, the results will be disseminated through local and international conferences. To date, results were presented at the European Congress of Clinical Microbiology and Infectious Diseases (April 2022), the General Practice Research on Infections Network (September 2022), the Congress of the European Geriatric Medicine Society (September 2022), and the North American Primary Care Research Group's Annual Meeting (November 2022). Also, materials for implementation in clinical practice will be developed and made available.

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Web appendix: Data supplement