Chapter 6
The effect of tailored antibiotic stewardship programmes on the appropriateness of antibiotic prescribing in nursing homes

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Abstract

Objectives: To evaluate the effect of tailored interventions on the appropriateness of decisions to prescribe or withhold antibiotics, antibiotic use, and guideline-adherent antibiotic selection in nursing homes (NHs).

Methods: We conducted a quasi-experimental study in 10 NHs in the Netherlands. A participatory action research (PAR) approach was applied, with local stakeholders in charge of selecting tailored interventions based on opportunities for improved antibiotic prescribing that they derived from provided baseline data. An algorithm was used to evaluate the appropriateness of prescribing decisions, based on infections recorded by physicians. Effects of the interventions on the appropriateness of prescribing decisions were analysed with a multilevel logistic regression model. Pharmacy data were used to calculate differences in antibiotic use, and recorded infections were used to calculate differences in guideline-adherent antibiotic selection.

Results: The appropriateness of 1,059 prescribing decisions was assessed. Adjusting for pre-test differences in the proportion of appropriate prescribing decisions (intervention: 82%, control: 70%), post-test appropriateness did not differ between groups (crude: p=0.26; adjusted for covariates: p=0.35). We observed more appropriate prescribing decisions at the start of data collection, and before receiving feedback on prescribing behaviour. No changes in antibiotic use or guideline-adherent antibiotic selection were observed in intervention NHs.

Conclusion: The PAR approach, or the way PAR was applied in the study, was not effective in improving antibiotic prescribing behaviour. The study findings suggest that drawing prescribers' attention to prescribing behaviour and monitoring activities, and increasing use of diagnostic resources may be promising interventions to improve antibiotic prescribing in NHs.

Introduction

Antibiotic stewardship programmes aim to optimize antibiotic therapy, thereby ensuring the best clinical outcomes while minimizing the development of antibiotic resistance.[1,2] The implementation of these programmes has been recommended in light of the global rise of antibiotic resistance and the association between the use of antibiotics and the emergence of antibiotic resistance.[3,4] Examples of antibiotic stewardship activities include audit and feedback, formulary restrictions, preauthorization, education, and guideline development. Whereas antibiotic stewardship programmes are increasingly being implemented in hospital care, they are relatively new to the long-term care setting.[1,2] This setting accommodates a population at increased risk of acquiring infections due to, for example, declined immune function, invasive device use, shared dining and social activities, and close contact with health care workers. Antibiotics are commonly prescribed in this setting, and part of it is potentially inappropriate.[2,5]

A few studies evaluated interventions to optimize antibiotic prescribing in long-term care facilities (LTCFs).[1,6–8] These studies varied in types of interventions, outcomes measured, and results. Due to this variation and several methodological limitations, two reviews reported that evidence regarding the effects of specific interventions is inconclusive.[1,6] Chances of success may have been limited because interventions were predetermined in these studies, while interventions may work in some contexts but not in other.[9–11] Indeed, antibiotic prescribing decisions depend on several local factors, which may vary between LTCFs. In a qualitative study we found that antibiotic prescribing behaviour in LTCFs is determined by the clinical situation, advance care plans, utilization of diagnostic resources, physicians' perceived risks, influence of others (e.g. family members, nursing staff), and several environmental factors (e.g. availability of guidelines).[12] It has been suggested that antibiotic prescribing improvement programmes are more likely to be effective if such factors are taken into account in the development of these programmes.[1,10,11,13,14]

In addition to addressing local facilitators and barriers, the involvement of local stakeholders may help in developing quality improvement programmes in health care.[15] We therefore hypothesize that participatory action research (PAR) is a suitable approach for the development of effective antibiotic stewardship programmes.[16] PAR is a research method that is characterized by the involvement of local stakeholders in the identification of opportunities for improved practice, the subsequent development and implementation of tailored interventions directed at these opportunities, and the evaluation of the implemented interventions. We studied the effect of tailored interventions developed with a PAR approach on the appropriateness of decisions to prescribe or withhold antibiotics (referred to as 'prescribing decisions') in nursing homes (NHs) in the Netherlands. In addition, we studied its effect on antibiotic use and on guideline-adherent antibiotic selection.

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Methods

Design and study setting

This mixed-methods, quasi-experimental, unblinded study aimed at improving appropriate antibiotic use in LTCFs: the Improving Rational Prescribing of Antibiotics in Long-term Care Facilities (IMPACT) study. We calculated the number of facilities and number of infections per facility needed for an 80% chance to detect a clinically meaningful increase of 15% in appropriateness of antibiotic prescribing,[8] adjusting for intraclass correlations of 0.03. This required 6 LTCFs in each group (i.e. intervention and control group), each delivering 98 recorded infections per data collection phase (i.e. pre-test and post-test), for a one-sided α of 0.05.

We intended to include 6 NHs and 6 residential care facilities (RCFs) in the study, but due to recruitment issues in RCFs, we included fewer RCFs (4) and more NHs (10). Further, as a consequence of the limited quality of data available from RCFs, the primary study outcome could not be determined for this setting. The current article therefore focuses on NHs only. To recruit NHs, physicians and managers of 9 individual NHs and 3 health care organizations were invited to participate in the study, as well as a university-affiliated network of 7 health care organizations.[17] All approached NHs and health care organizations were located in the central-west region of the Netherlands for practical reasons (a nationally representative sample was not pursued due to the relatively small number of LTCFs required for the study). NHs that participated in other infectious diseases-related projects were excluded from participation in the study.

Dutch NHs employ elderly care physicians (formerly called nursing home physicians), which is a distinct medical specialty in the Netherlands. These physicians have the NH as their main site of practice.[18] Dutch NHs accommodate residents on three types of care units: somatic units (for physically disabled residents), psychogeriatric units (mostly for residents with dementia), and rehabilitation units.[19]

Facilities were allocated to either the intervention group or the control group (each comprising 5 NHs), thereby ensuring; 1) a comparable number of residents in each group, 2) that facilities affiliated with the same healthcare organization were assigned to the same group, and 3) that each group included facilities with higher and lower antibiotic use at baseline. The latter was based on data on prescriptions of drugs of Anatomical Therapeutical Chemical (ATC) class J01 (i.e. antibacterials for systemic use) for residents of the NH between July 1st 2010 and June 30th 2011, as provided by facility-affiliated pharmacies.

Data collection

Physicians completed a form for each case in which they – based on their clinical judgment – suspected a urinary tract infection (UTI), respiratory tract infection (RTI),

or skin infection (SI). The form was based on relevant guidelines and literature, and included documentation of patient characteristics (e.g. age, sex, wheelchair dependence), vital signs in the past 48 hours (e.g. blood pressure, pulse, temperature), recent/current health status (e.g. new or worsening confusion, decreased intake), medical history (e.g. diabetes, COPD, dementia), signs and symptoms related to the suspected infection type, and details of the treatment decision (i.e. antibiotic prescribing including details on the prescription, or no antibiotic prescribing including the reason for not prescribing). Infections were recorded over the same 8-month periods in 2012 and 2013. In 9 NHs, this period occurred between January and October. In one NH, due to organizational issues, data collection was delayed and occurred between April and December. The physicians recorded infections as soon as possible after the diagnosis, and regardless of whether antibiotics were prescribed. Recurring infections were also included. Only infections diagnosed in the NH were included. In case an infection was diagnosed by an on-call physician not employed by the NH, the physician responsible for the care of the patient completed the recording form based on the descriptions (e.g. in the medical chart) of the on-call physician.

To assess overall antibiotic use in the participating facilities, pharmacies affiliated with the facilities provided an overview of all drugs of ATC class J01 (i.e. antibacterials for systemic use) prescribed for residents of the NH between January 1st and September 30th in 2012 and 2013. These overviews included drug names, prescription dates, and information on duration and dosing for each individual prescription. To link the pharmacy data to the number of resident-care days in the facilities, the NHs provided information on size (number of beds) and bed occupancy per care unit.

Outcomes
The primary outcome, appropriateness of decisions to prescribe or withhold antibiotics, was evaluated for each infection by applying an algorithm (one for each infection type, i.e. UTI, RTI, and SI) to the recording forms. This algorithm was developed with input from a national expert panel, and was based on diagnostic criteria described in national and international guidelines. Detailed procedures and the algorithms can be found elsewhere.[17] Secondary study outcomes included antibiotic use and guideline-adherent antibiotic selection.

Intervention
Tailored interventions were selected, developed and implemented in the intervention NHs during the 4 months between the end of the pre-test phase and the start of the post-test phase (in the control NHs, this occurred after the post-test phase). A PAR approach was applied for the selection, development, and implementation of interventions directed at appropriate antibiotic prescribing. This approach is characterized by the involvement of local stakeholders in a cyclical process including: 1) the identification of opportunities for improved practice (i.e. planning action), 2)

the development and implementation of tailored interventions directed at these opportunities (i.e. taking action), and 3) the evaluation of the implemented interventions (i.e. reflecting on action). The use of the approach in the current study is described in short below, and in more detail elsewhere.[16]

After completion of the pre-test phase, 1.5 to 2-hour multidisciplinary meetings were held in each intervention NH. This meeting included 5 to 6 members of the project team (i.e. the researchers and advisors of the Dutch Institute for Rational Use of Medicine) and 5 to 9 local stakeholders including physicians, nursing staff, pharmacists, and managerial staff. Researchers presented local pre-test prescribing in comparison with overall pre-test data, and qualitative data on factors influencing antibiotic prescribing behavior.[12] Next, project team members moderated focus group discussions, aimed at discussing the pre-test data and identifying local facilitators, barriers, and opportunities to improve appropriate antibiotic prescribing. These opportunities were prioritized in a plenary discussion, followed by the selection of interventions addressing the opportunities with the highest priorities (step 1 of the PAR cycle: planning action). In the next months, tailored interventions were developed and implemented by the local stakeholders in collaboration with the project team (step 2 of the PAR cycle: taking action). Table 1 provides an overview of the implemented interventions.

Process evaluation

After completion of the post-test phase, a researcher (LB) fed back the study results in each intervention NH, during meetings with 2 to 10 local stakeholders, including physicians, nursing staff, and managerial staff. Next, a discussion was facilitated aimed at exploring local stakeholders' responses, conclusions, and explanations with regard to the study results. This process evaluation meeting constituted the third step of the PAR cycle, i.e. reflecting on action.

Data analysis

The data on the infection recording forms were entered into a Microsoft Access 2000 database (Microsoft Corporation, Redmond, WA, USA) by two persons independently. Subsequently, the data were processed in SPSS version 20 (IBM Corporation, New York, NY, USA). We used descriptive statistics to summarize the data. Chi-square tests, t-tests, and Mann-Whitney U-tests were employed to analyse between-group differences in demographic characteristics and within-group differences in appropriateness of prescribing decisions (this dichotomous variable was created based on the algorithm outcomes[17]). The latter was also analysed in a subgroup with physicians who participated in both the pre-test and the post-test phase, to exclude a potential influence of physician turnover. We examined between-group differences in appropriateness of prescribing decisions (overall, and in different subgroups: 1) the post-test phase subdivided in periods of 2 months, 2) only physicians who

Table 1: Interventions selected by nursing homes in the intervention group, by category.

Intervention	NH-1	NH-2	NH-3	NH-4	NH-5
Improving physician knowledge: guideline discussion meetings and/or knowledge tests					
Focus	RTI	UTI	UTI & RTI	RTI	UTI
Participants (n)	3	4	2	5	6
Timing of implementation	in intervention phase	in intervention phase	in intervention phase	within 2 weeks after intervention phase	within 1 month after intervention phase
Improving physician - nursing staff communication					
Multidisciplinary meetings					
Focus	RTI	UTI			
Participants (n)	5	8			
Timing of implementation	in intervention phase	in intervention phase			
Nursing staff education (1-hour meetings) on infections in general, antibiotics, antibiotic resistance, UTI & RTI					
Participants (n)	8		29	10	65
Timing of implementation	within 1 month after intervention phase	within 1 month after intervention phase	within 2 weeks after intervention phase	within 1 month after intervention phase	2 sessions in intervention phase, 3 sessions within 2 months after intervention phase
Protocol for nursing staff on recognition, registration and communication of signs and symptoms in residents					
Timing of implementation				within 2 months after intervention phase	throughout the post-test phase
Optimizing medication formularies: pharmacotherapy counselling meetings					
Focus	UTI	UTI	UTI & RTI	RTI	UTI
Participants (n)	5	8	2	5	6
Timing of Implementation	end of the post-test phase		In Intervention phase	within 2 weeks after intervention phase	within 1 month after intervention phase
Understanding local UTI resistance patterns: evaluation of new/previous urine culture results					
Timing of implementation		within 2 months after intervention phase		in intervention phase	within 1 month after intervention phase
Increasing utilization of diagnostic resources: agreement to take cultures more regularly					
Timing of implementation					in intervention phase
Improve collaboration with cross coverage group : agreement to follow the facility's local formulary when on call					
Timing of implementation				within 2 months after intervention phase	

Abbreviations: NH= nursing home, RTI= respiratory tract infection, UTI= urinary tract infection.

In NH2, NH3, NH4, and NH5, activities directed at improving physician knowledge were integrated into pharmacotherapy counselling meetings (duration 1 to 2 hours). In NH2, pharmacotherapy counselling meetings were also combined with a multidisciplinary meeting aimed at improving physician-nursing staff communication. In NH1, a multidisciplinary meeting (duration 1 hour) aimed at improving physician-nursing staff communication was combined with activities directed at improving physician knowledge.

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participated in both data collection phases, and 3) only infections treated with antibiotics), by using multilevel logistic regression analyses with the outcome variable modelled as a function of group and time, accounting for pre-test differences between both groups. The clustering in the data was accounted for by a random intercept at the NH level and the resident level. We applied a second-order penalized quasi-likelihood estimation procedure, using MLwiN version 2.30 (Centre for Multilevel Modelling, University of Bristol, Bristol, UK). In an additional analysis, all patient demographic characteristics were added to the model as covariates. Because there were more than 5% missing values for some covariates (i.e. urinary incontinence, length of stay, dementia, wheelchair-dependence, and urinary catheter), we performed multiple imputation using the Markov Chain Monte Carlo method in SPSS version 20 (IBM Corporation, New York, NY, USA). In line with published recommendations, we imputed only the covariates and not the outcome variable.[20] Five imputations were performed, and results were pooled according to Rubin's rules.[21] The adjusted analyses presented in this article are based on the model with imputed data, while sensitivity analyses were performed on the dataset without imputed covariates. For all analyses, the significance level was a priori set at $p < 0.05$ ($p < 0.10$ was considered a marginally significant difference).

Pharmacy data were used to calculate the number of therapeutic antibiotic prescriptions and defined daily doses (DDDs; therapeutic and prophylactic) per 1,000 resident-care days (using the number of beds in the facility multiplied by their occupancy rate). DDDs were calculated using the WHO ATC/DDD Index 2014. Mean incidences of therapeutic prescriptions and DDDs were used to calculate a combined incidence for the intervention group and control group. Data on the infection recording forms were used to calculate the percentage of total prescriptions that was guideline-adherent, separately for RTI and for UTI in residents with and without a catheter (we excluded SI because of small numbers of cases for this infection type). A guideline-adherent prescription was defined as prescribing the first-choice antibiotic for the clinical indication (i.e. RTI: amoxicillin; UTI with catheter: fluoroquinolones; UTI without catheter: nitrofurantoin, trimethoprim or trimethoprim/sulfamethoxazole), based on relevant national prescribing guidelines (for RTI the guideline 'acute cough' [2011] of the Dutch College of General Practitioners, and for UTI the guidelines 'urinary tract infections' [2006] and 'urinary catheters' [2011] of the Dutch Association of Elderly Care Physicians and Social Geriatricians). Due to the small number of cases per group (5), we did not test between-group differences in incidence of therapeutic prescriptions, incidence of DDDs, and change in guideline-adherent selection of antibiotics.

Ethics approval
All study procedures were reviewed and approved by the Medical Ethics Review Committee of the VU University Medical Center (Amsterdam, the Netherlands) prior

to study commencement. The IMPACT study is registered in The Netherlands National Trial Register (ID number NTR3206).

Results

The ten participating NHs had a mean number of 162 beds per facility (range: 68 – 219) and a mean bed occupancy of 96% (range: 90% - 100%). On average, 51% of the beds were for psychogeriatric patients (i.e. mostly with dementia; range: 0% - 78%), 33% for somatic patients (i.e. with physical disability; range: 21% - 72%), and 16% for rehabilitation patients (range: 0% - 35%). Demographic characteristics of residents and differences between and within groups are summarized in Table 2.

Table 2. Resident characteristics of recorded infections, per data collection phase and group.

Characteristic	Pre-test		Post-test	
	Intervention (n=328)	Control (n=379)	Intervention (n=275)	Control (n=277)
Sociodemographic				
Female, n/N (%)	232/328 (70.7)	279/379 (73.6)	188/275 (68.4)	209/277 (75.5)
Age; n, mean (range)	325, 83.3 (50.0 – 100.0)	378, 83.7 (43.0 – 101.0)	275, 82.9 (53.0 – 102.0) [a]	276, 84.8 (46.0 – 100.0) [a]
Length of stay (months); n, median (range)	307, 7.0 (0.0 – 180.0)	342, 9.0 (0.0 – 191.0)	260, 11.0 (0.0 – 146.0)	243, 12.0 (0.0 – 141.0)
Type of unit, n/N (%)				
Somatic	133/327 (40.7) [b]	127/378 (33.6) [b]	122/273 (44.7) [a]	110/273 (40.3) [a]
Psychogeriatric	120/327 (36.7) [b]	198/378 (52.4) [b]	90/273 (33.0) [a]	128/273 (46.9) [a]
Rehabilitation	74/327 (22.6) [b]	53/378 (14.0) [b]	61/273 (22.3) [a]	35/273 (12.8) [a]
Functioning, n/N (%)				
Wheelchair-dependent	200/316 (63.3) [b]	174/342 (50.9) [b]	183/263 (69.6) [a]	144/258 (55.8) [a]
Urinary catheter	56/318 (17.6)	50/353 (14.2)	43/261 (16.5)	46/259 (17.8)
Urinary incontinence [c]	213/285 (74.7)	234/310 (75.5) [d]	170/233 (73.0) [a]	190/226 (84.1) [a,d]
Comorbidities, n/N (%)				
Diabetes mellitus	66/320 (20.6)	67/362 (18.5)	51/270 (18.9)	58/267 (21.7)
Chronic obstructive pulmonary disease	44/320 (13.8)	64/356 (18.0)	27/268 (10.1) [a]	43/267 (16.1) [a]
Dementia	130/304 (42.8) [b]	210/353 (59.5) [b,d]	99/256 (38.7) [a]	132/265 (49.8) [a,d]

[a] *Significant between-group difference during post-test phase;* [b] *Significant between-group difference during pre-test phase;* [c] *The physicians sometimes did not know whether a residents was incontinent for urine or not, which explains the relatively high number of missings on this variable;* [d] *Significant difference within groups between pre-test and post-test phase.*

Appropriateness of decisions to prescribe or withhold antibiotics

Sufficient data from the infection recording forms were available to evaluate appropriateness of 1,059 (84%) of the 1,259 prescribing decisions (intervention: 278 pre-test, 233 post-test; control: 320 pre-test, 228 post-test). These 1,059 infections occurred in a total of 774 residents. Of the prescribing decisions, 59% were for UTIs, 34% for RTIs, and 7% for SIs. Antibiotics were prescribed in 88% of the cases (intervention: 91%; control: 86%) in the pre-test phase, and in 90% of the cases (intervention: 92%; control: 90%) in the post-test phase.

Table 3A shows that there was no pre-post-test difference in appropriate prescribing decisions in the intervention group (from 82% pre-test to 79% post-test; p=0.28), whereas appropriateness in the control group increased marginally (from 70% to 77%; p=0.06). A similar pattern was observed in a subgroup analysis for UTI, whereas for RTI, there was no pre-post-test difference in appropriateness in both groups (Table 3A). The increase in appropriate prescribing decisions overall and for UTI in control group facilities was attributable to physician turnover; the effect disappeared when

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only physicians who participated in both the pre-test and the post-test phase were included in the analysis (overall: n=372, from 72% to 73% (p=0.85); UTI: n=231, from 64% to 68% (p=0.63).

Table 3. Appropriateness of antibiotic prescribing decisions, per group and data collection phase (A), and effect of the intervention on appropriateness of antibiotic prescribing decisions, with the control group as reference group (B).

	A) Within-group appropriateness of antibiotic prescribing decisions						B) Effect of the intervention			
	Intervention			Control			Unadjusted		Adjusted[a]	
	Pre-test	Post-test	p-value	Pre-test	Post-test	p-value	OR	95% CI	OR	95% CI
Overall	82%	79%	0.28	70%	77%	0.06	0.71	(0.40;1.28)	0.76	(0.43;1.34)
UTI	77%	72%	0.42	61%	74%	0.01	0.68	(0.35;1.31)	0.74	(0.39;1.40)
RTI	89%	82%	0.20	84%	83%	0.81	0.97[†]	(0.42;2.27)	0.95[b]	(0.39;2.33)

OR, odds ratio; CI, confidence interval; UTI, urinary tract infection; RTI, respiratory tract infection.
[a] Adjusted for: sex, age, length of stay, type of unit, wheelchair dependency, urinary catheter, urinary incontinence, diabetes mellitus, chronic obstructive pulmonary disease, dementia.
[b] A first order maximum quasi-likelihood estimation procedure was used for this subgroup analysis, due to small numbers.

There was no effect of the interventions on the appropriateness of prescribing decisions overall, and for UTI and RTI separately, both in the unadjusted and adjusted multilevel model (Table 3B). The same was true in a subgroup analysis with the post-test phase subdivided in periods of 2 months, with only physicians who participated in both data collection phases, and with only infections treated with antibiotics (data not shown). The sensitivity analyses similarly showed no effect of the intervention.
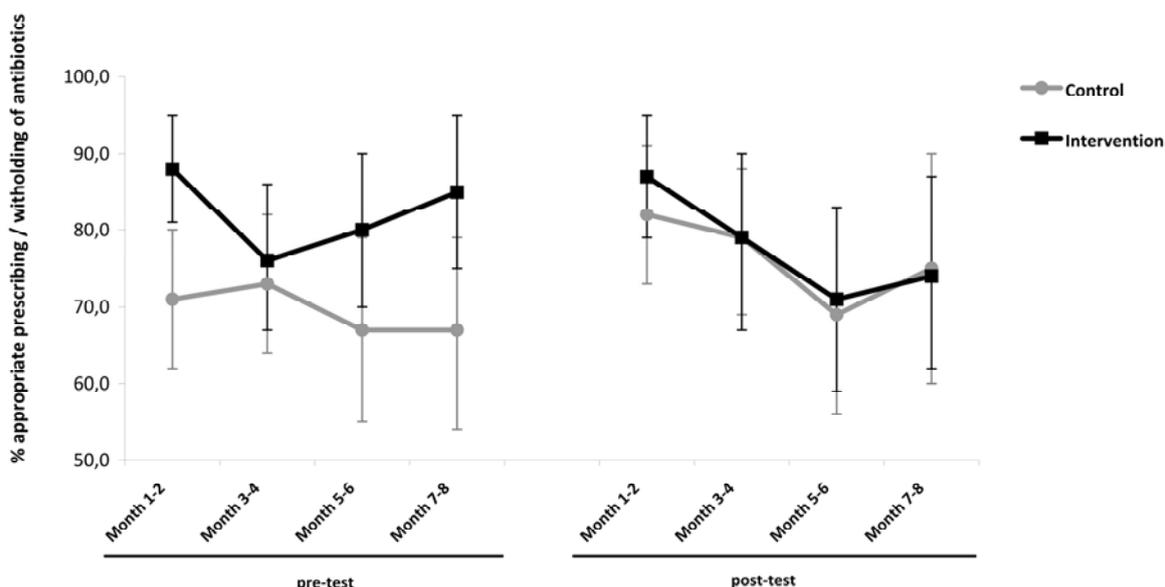

Figure 1. Percentage appropriate antibiotic prescribing decisions in the intervention and control group over time, with the 8-month pre-test and post-test phase subdivided into two-month intervals.

Figure 1 displays the proportions of appropriate prescribing decisions in the intervention and control group over time, for all infections. The figure shows relatively high levels of appropriate prescribing decisions in both groups at the start of each data collection phase, which was preceded by a meeting to introduce the study goals and data collection procedures. The increased levels at the end of each data collection

phase corresponded with the time it was announced that prescribing feedback would be provided shortly (to the intervention group in both data collection phases and to the control group only in the post-test phase). A similar 'u-shape' was observed in a subgroup analysis with only physicians who participated in both data collection phases (data not shown).

Antibiotic use and guideline-adherent antibiotic selection
Table 4 shows the mean antibiotic use in the intervention group and control group during the pre-test and post-test phase. The number of therapeutic prescriptions per 1.000 resident-care days increased in both groups (with 0.6 prescriptions in the intervention group and 0.3 prescriptions in the control group). The total number of DDDs decreased with 2.3 DDDs per 1.000 resident-care days in intervention facilities, and increased with 1.1 DDDs per 1.000 resident-care days in control facilities.

Table 4. Mean antibiotic use pre-test and post-test in the intervention group and control group.

	n	Therapeutic antibiotic prescriptions / 1,000 resident-care days			Total DDD / per 1,000 resident-care days		
		Pre-test	Post-test	Difference (range)	Pre-test	Post-test	Difference (range)
Intervention	5	5.5	6.1	+ 0.6 (-0.3;1.4)	62.3	60.0	- 2.3 (-11.4;6.8)
Control	5	4.6	4.9	+ 0.3 (-1.4;1.7)	46.2	47.3	+ 1.1 (-13.1;18.2)

The percentage guideline-adherent antibiotic selection, per group and data collection phase, is displayed in table 5. Guideline-adherent antibiotic selection increased comparable in both groups for RTI (intervention: 0.8%, control: 1.6%) and for UTI in residents without a catheter (intervention: 8.3%, control: 5.1%). For UTI in residents with a catheter, there was a stronger increase in guideline-adherent antibiotic selection intervention facilities (15.9%) compared to control facilities (1.8%), however, the number of cases was small for this clinical situation.

Table 5. Percentage guideline-adherent antibiotic selection[*] per indication, per group and data collection phase.

Indication		Intervention		Control	
		n/N	%	n/N	%
UTI with catheter	Pre-test	7/28	25.0	3/24	12.5
	Post-test	9/22	40.9	4/28	14.3
	Difference		+ 15.9		+ 1.8
UTI without catheter[*]	Pre-test	58/124	46.8	85/178	47.8
	Post-test	65/118	55.1	64/121	52.9
	Difference		+ 8.3		+ 5.1
RTI[*]	Pre-test	10/110	9.1	7/92	7.6
	Post-test	8/81	9.9	7/76	9.2
	Difference		+ 0.8		+ 1.6

UTI, urinary tract infection; RTI, respiratory tract infection.
*Prescribing of first-choice antibiotics as recommended in national guidelines. For UTI with catheter: fluoroquinolones, for UTI without catheter: nitrofurantoin, trimethoprim, or trimethoprim/sulfamethoxazole, for RTI: amoxicillin.

Process evaluation
During the process evaluation meetings, the local stakeholders mentioned several possible explanations for the absence of an intervention effect on appropriateness of antibiotic prescribing decisions. These included a 'ceiling effect' (i.e. the impossibility to further improve the already high level of appropriate prescribing decisions at baseline), a lack of motivation to improve prescribing behaviour, physician turnover,

and the failure of selected interventions to sufficiently change prescribing behaviour. These explanations are further elaborated in Figure 2.

- A **'ceiling effect'**: the level of approximately 80% appropriate prescribing decisions may be the best achievable, as it is not possible for prescribing decisions to be 100% in accordance with diagnostic guidelines. This is considered to be due to the complex patient population, where uncertainty regarding the clinical presentation is common, and as a consequence other factors than indicated in the guidelines may be involved in decision-making (e.g. perceived risks of non prescribing, a lack of diagnostic resources, expectations of patients, family, and nursing staff).(*5/5 meetings*)
- **Lack of motivation** to improve appropriate prescribing, as a consequence of: 1) the high pre-test level of appropriate prescribing decisions (*3/5 meetings*), 2) organizational issues(*1/5 meetings*) or 3) the long duration of data collection.(*1/5 meetings*)
- **Physician turnover** in the facility, complicating the improvement of prescribing practices.(*2/5 meetings*)
- The selected **interventions did not succeed in adapting prescribing behaviour**.(*1/5 meetings*)

Figure 2. Local stakeholders' explanations for the absence of an intervention effect on appropriateness of antibiotic prescribing decisions.

Discussion

It has been emphasized that local stakeholders should be involved in the development of antibiotic stewardship programmes, and that local barriers, facilitators and opportunities should be addressed.[1,6,10,11,13,14,22] Despite the incorporation of the aforementioned in our PAR approach, we found no effect of tailored interventions on the appropriateness of decisions to prescribe or withhold antibiotics in NHs in the Netherlands. Similarly, we did not find an intervention effect on antibiotic use or guideline-adherent antibiotic selection.

The baseline level of approximately 80% appropriate antibiotic prescribing decisions in intervention NHs may suggest little room for improvement a priori. Study participants, as they commented in retrospect, regarded this high baseline performance as a possible 'ceiling' of the extent to which antibiotics can be prescribed in accordance with diagnostic guidelines. However, although this percentage is higher than reported previously (i.e. 44% to 74%),[7,23–29] our study suggests that further improvement in appropriate prescribing decisions would have been possible. Levels of appropriate prescribing decisions were lower for UTI compared to RTI and SI, with asymptomatic bacteriuria a common situation in which antibiotics were prescribed inappropriately.[17] This suggests room for improvement by reducing treatment for asymptomatic bacteriuria. In addition, qualitative interviews with study participants showed several questionable reasons for antibiotic prescribing, such as prescribing to avoid perceived risks ('better safe than sorry') or prescribing on request of patients, family members, or nursing staff.[12] Appropriate prescribing may increase if the influence of such factors is reduced. Finally, the current study found higher levels of appropriate prescribing decisions at times the researchers drew attention to antibiotic prescribing behaviour and the monitoring activities. Hence, there was no stable level of appropriate prescribing decisions that may represent the highest possible level of appropriateness, and this indicates that improvement of appropriate prescribing decisions may have been possible.

The absence of an intervention effect may be explained by PAR not being a suitable approach for the development and implementation of interventions that are effective in improving antibiotic use, despite its advantage of addressing local facilitators and barriers. A possible limitation of the approach is its voluntary nature. It has been reported that enforced compliance with antibiotic treatment guidelines is more effective than voluntary compliance, and that pre-set targets and action plans facilitate effectiveness of audit and feedback.[30,31] In PAR, the selection of interventions depends upon the motivation and involvement of local stakeholders. Although the issue was raised in retrospect in our study, a high baseline performance may temper motivation to undertake action to improve practice, and physician turnover may affect participants' involvement in the study.

Alternatively, not the PAR approach itself, but the way in which the approach was applied in the current study, may have resulted in the absence of an intervention effect. First, due to time restrictions, we conducted only one PAR cycle of planning action, taking action, and reflecting on action. However, these cycles should ideally be repeated until the desired outcomes are achieved.[16] In addition, time-consuming interventions may have been avoided due to the pre-determined period of four months for the selection, development, and implementation of tailored interventions. The selection of interventions may have also been affected by the limited project budget. For example, no financial contributions could be made to the purchase of diagnostic resources. These restrictions may have resulted in a suboptimal application of the PAR approach in the current study.

We indeed encountered the abovementioned time and budget restrictions in the development and implementation of interventions in the current study. Three intervention NHs intended to increase the use of diagnostic resources, of which one succeeded in taking urine cultures more regularly. The other two NHs explored possibilities to purchase on-site diagnostic resources (i.e. C-reactive protein point-of-care test, uricult), but they did not succeed in their implementation due to the long time required by the organizations' management to decide on the purchase of such equipment and the absence of financial support. Consequently, no on-site diagnostic resources were implemented in these NHs within the study period.

Increasing the use of diagnostic resources may, however, be a successful intervention to improve appropriateness of antibiotic prescribing. The NH that decided to take urine cultures more regularly was the only facility where appropriateness of antibiotic prescribing for UTI increased (from 66% to 74%). The implementation of diagnostic tools has also improved antibiotic use in primary care studies.[32,33] The use of diagnostic resources can reduce diagnostic uncertainty, which is common in NHs due to impaired communication in residents and atypical presentation of symptoms.[34,35] In such uncertain clinical situations, the risk of unjustly withholding of antibiotics may outweigh the risks of unjust antibiotic prescribing, as antibiotic withholding may have

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severe consequences in the vulnerable NH population (i.e. deterioration or death).[12] As it may be difficult to change such risk perceptions in uncertain clinical situations, increasing the use of diagnostic resources to decrease diagnostic uncertainty may be a more feasible intervention to improve appropriateness of antibiotic prescribing.

Due to small numbers of cases we did not statistically test between-group differences in antibiotic use nor differences in the percentages of guideline-adherent antibiotic selection. Nevertheless, the findings do not indicate a relevant decrease in antibiotic use in intervention versus control NHs. This corresponds with a study by Loeb et al.,[36] in which the effect of a multifaceted intervention was evaluated, but contradicts other studies that reported a decrease in antibiotic prescriptions following intervention implementation.[8,37,38] With regard to antibiotic selection for RTI, the guidelines recommend amoxicillin as the first-choice antibiotic, but in case of aspiration pneumonia, amoxicillin/clavulanate is recommended. As we did not collect data on the suspected origin of pneumonia (i.e. aspiration or other), we are not able to comment on the degree of guideline-adherent antibiotic selection for this type of infection. Regarding UTI in residents without a catheter, the study findings do not suggest increased guideline-adherent antibiotic selection in intervention versus control NHs. A study that evaluated the effect of a multifaceted intervention similarly did not find an increase in guideline-adherent antibiotic selection,[39] but some others reported a positive effect of different interventions on guideline-adherent prescribing patterns.[37,38,40,41] Considering the variety of interventions and the inconclusive results, more research is needed to elucidate which interventions can effectively reduce antibiotic use and promote guideline-adherent antibiotic selection in LTCF.[6]

Only a few LTCF studies evaluated appropriateness in terms of whether there is an indication for antibiotic prescribing,[7,23–29] however, our study is, to our knowledge, the first to evaluate the effect of an intervention on this outcome measure in NHs. In addition, whereas these previous studies only focused on appropriateness of antibiotic prescribing, we also included infections that were not treated with antibiotics in our evaluation of appropriateness of prescribing decisions. Some limitations also apply to our study. First, as reported in our publication of the pre-test results of the study,[17] chart review revealed that more than half of the infections were not recorded by physicians on the study forms (with a variation of 37% to 78% between NHs), mainly due to physicians forgetting to complete a form when the infection was diagnosed outside of working hours, when a form was recently completed for the same patient, and when no antibiotic was prescribed. There were, however, no reasons to assume that infections recorded by physicians differed substantially from those not recorded, as patient characteristics and the distribution of infection types were comparable between recorded and non-recorded infections. Second, several interventions were not implemented within the planned timeframe of four months (Table 1). Nevertheless, the post-test findings do not indicate a delayed effect of these interventions. Further, inherent to the PAR approach that produces a

set of interventions tailored to the needs of each facility, we could not determine effects of single intervention components. Finally, as data collection issues in RCFs led to the exclusion of this type of long-term care setting in the current analyses, we included fewer facilities than pre-determined by our power calculation (5 instead of 6 per group).

To conclude, we found no effect of tailored interventions developed with a PAR approach on the appropriateness of decisions to prescribe or withhold antibiotics in NHs in the Netherlands. Despite the high level of appropriate prescribing decisions a priori, the study findings indicate that further improvement would have been possible, particularly for UTI. The PAR approach itself, or the way PAR was applied in the current study, was not effective in improving antibiotic prescribing behaviour. More research is needed to elucidate how antibiotic stewardship programmes can be effectively implemented in LTCFs, in addition to research on which intervention components are effective in improving antibiotic prescribing behaviour. Based on the current study, drawing prescribers' attention to antibiotic prescribing behaviour and monitoring activities, and increasing use of diagnostic resources may be promising interventions to improve antibiotic prescribing behaviour.

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