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Cost-effectiveness and return-on-investment of C-reactive protein point-of-care testing in comparison with usual care to reduce antibiotic prescribing for lower respiratory tract infections in nursing homes: a cluster randomised trial

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ABSTRACT

Objectives C-reactive protein point-of-care testing (CRP POCT) is a promising diagnostic tool to guide antibiotic prescribing for lower respiratory tract infections (LRTI) in nursing home residents. This study aimed to evaluate cost-effectiveness and return-on-investment (ROI) of CRP POCT compared with usual care for nursing home residents with suspected LRTI from a healthcare perspective.

Design Economic evaluation alongside a cluster randomised, controlled trial.

Setting 11 Dutch nursing homes.

Participants 241 nursing home residents with a newly suspected LRTI.

Intervention Nursing home access to CRP POCT (POCT-guided care) was compared with usual care without CRP POCT (usual care).

Main outcome measures The primary outcome measure for the cost-effectiveness analysis was antibiotic prescribing at initial consultation, and the secondary outcome was full recovery at 3 weeks. ROI analyses included intervention costs, and benefits related to antibiotic prescribing. Three ROI metrics were calculated: Net Benefits, Benefit-Cost-Ratio and Return-On-Investment.

Results In POCT-guided care, total costs were on average €32 higher per patient, the proportion of avoided antibiotic prescribing was higher (0.47 vs 0.18; 0.30, 95% CI 0.17 to 0.42) and the proportion of fully recovered patients statistically non-significantly lower (0.86 vs 0.91; −0.05, 95% CI −0.14 to 0.05) compared with usual care. On average, an avoided antibiotic prescription was associated with an investment of €137 in POCT-guided care compared with usual care. Sensitivity analyses showed that results were relatively robust. Taking the ROI metrics together, the probability of financial return was 0.65.

Conclusion POCT-guided care effectively reduces antibiotic prescribing compared with usual care without significant effects on recovery rates, but requires an investment. Future studies should take into account potential beneficial effects of POCT-guided care on costs and health outcomes related to antibiotic resistance.

Trial registration number NL5054.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To our knowledge, this is the first study to evaluate cost-effectiveness of point-of-care C-reactive protein testing versus usual care to reduce antibiotic prescribing for nursing home residents with suspected lower respiratory tract infections.
⇒ The economic evaluation was conducted with data that 84 physicians from 11 nursing homes collected for 241 participants with a newly suspected lower respiratory tract infection.
⇒ Strengths of the current study are the adjustment for clustering and concordance with the effectiveness analysis.
⇒ Limitations of the study are the healthcare instead of societal perspective, the short follow-up period and that a cost–utility analysis could not be performed.

BACKGROUND

Lower respiratory tract infections (LRTI) frequently occur in the nursing home setting and range from less severe acute bronchitis to more severe illness such as pneumonia.[1 2] The health of residents with pneumonia can deteriorate rapidly given the general frailty of this population.[3 4] Consequently, pneumonia is associated with increased morbidity, and high mortality and hospitalisation rates.[2 5–9] In addition, hospitalisation for pneumonia can generate substantial healthcare costs.[6 8 10] For

example, in French nursing homes 68% of mean annual additional cost for incident pneumonia was attributed to hospitalisations.[11] However, assessment of the presence and severity of LRTI is complicated by atypical clinical presentation and limited availability of diagnostic resources in nursing homes.[3 12 13] This diagnostic uncertainty is a challenge for physicians when identifying patients who potentially benefit from antibiotic treatment.[12 14] On the patient level, prompt and appropriate treatment with antibiotics is essential to reduce the risk of increased morbidity, mortality and hospitalisation associated with the LRTI.[3 5 9] On the societal level, conversely, overprescribing to be 'better safe than sorry' is undesirable, as unnecessary antibiotic treatment contributes to the development of antimicrobial resistance.[12 15 16]

C-reactive protein point-of-care testing (CRP POCT) is a promising diagnostic tool to guide antibiotic prescribing decisions for suspected LRTI in nursing homes. CRP is a dynamic, non-specific biomarker that indicates the presence and severity of inflammation.[17 18] The consideration of CRP, together with clinical signs and symptoms, could guide antibiotic prescribing decisions by reducing uncertainty regarding the likelihood of severe versus less severe LRTI.[19–22] In general practice, CRP POCT was proven (cost-)effective compared with usual care in reducing antibiotic prescribing for suspected LRTI.[23–25] In addition, results from the recently completed UPCARE (Using Point-of-care C-reactive protein to guide Antibiotic prescribing for Respiratory tract infections in Elderly nursing home residents) trial similarly show that the use of CRP POCT effectively reduces antibiotic prescribing for suspected LRTI in the nursing home setting, compared with care in the control group.[26] However, it is important for policymakers and nursing home management to also know whether the use of CRP POCT would be an efficient use of resources, before further implementation steps are undertaken. Although an initial investment is needed, prompt identification and treatment of severe LRTI using CRP POCT might reduce risk of hospitalisation, which incurs the largest part of costs related to LRTI in the nursing home.[5 8 11] Also, a potential side effect of CRP POCT use might be that other, more expensive diagnostic tools such as thoracic imaging or laboratory tests are used less frequently.

Therefore, the aim of this study is to evaluate the cost-effectiveness and return-on-investment of CRP POCT use in comparison with usual care without CRP POCT for nursing home residents with suspected LRTI from a healthcare perspective. In this economic evaluation, we assess whether the use of CRP POCT for suspected LRTI results in reduced antibiotic prescribing, without negative clinical or economic consequences.

METHODS

Trial design

This economic evaluation was conducted alongside a pragmatic cluster randomised controlled trial (UPCARE study) that compared availability of CRP POCT (POCT-guided care) in the intervention group with usual care without CRP POCT (usual care) in the control group for nursing home residents with suspected LRTI. The trial took place from September 2018 until April 2020 in 11 nursing homes across the Netherlands. Randomisation with 1:1 ratio resulted in six organisations providing POCT-guided care and five organisations providing usual care. The trial was registered at the Netherlands Trial Register on 29 August 2018. The full protocol is described elsewhere.[27]

Patient and public involvement

The patients and public were not involved in the development of the study design and research questions. Some client councils of participating nursing homes reviewed the information letter before study commencement.

Setting

Dutch nursing homes are heterogeneous with regard to scale (ie, ranging from large apartment buildings to residential small-scale living) and type of specialised care they provide for their residents. Nursing home organisations in the UPCARE study participated with two to four locations, which had on average 122 residents (range: 26–230) each. Most Dutch nursing homes employ specialised 'elderly care physicians' that have their principal site of practice within the nursing home. Also, it is common policy in Dutch nursing homes to limit the use of intravenous drugs and hospital referrals.[28–30]

Study population

Residents from somatic, psychogeriatric and short-stay (geriatric rehabilitation and short-term residential care) wards suspected of having an LRTI were eligible for participation. Exclusion criteria were a recorded statement to withhold antibiotic treatment, or current/recent (ie, in the past week) infection or antibiotic treatment. Before the start of the trial, all residents received a trial information letter with the possibility to opt-out for participation. Written informed consent was asked only from residents who were eligible for participation and who did not previously opt-out.

Trial procedures

Data collection

Physicians collected data on the participants using electronic case report forms (eCRFs) that were integrated in the nursing home electronic patient record system. For each participant, physicians filled out one baseline eCRF (at initial consultation) and two follow-up eCRFs (1 week and 3 weeks later) with questions regarding clinical status, additional diagnostics and management decisions.

Intervention

CRP POCT devices (QuikRead go, Aidian, Espoo, Finland) were provided to the nursing homes allocated to the intervention group by primary care diagnostic centre Saltro (Unilabs, Utrecht, the Netherlands) for

Table 1 Baseline characteristics of the study population presented in N (%) unless specified otherwise

Patient characteristics	POCT-guided care, N (%)* N=162	Usual care, N (%)* N=79
Age in years, mean (SD)	84.3 (8.1)	84.5 (8.4)
Females	104 (64)	49 (62)
Nursing home ward		
Psychogeriatric	55 (35)	23 (29)
Somatic	71 (45)	42 (53)
Geriatric rehabilitation	29 (18)	11 (14)
Short-term residential care	3 (2)	3 (4)
Comorbid diseases		
Acute ischaemic stroke	32 (20)	15 (19)
Congestive heart failure	50 (31)	19 (24)
Chronic obstructive pulmonary disease	47 (30)	29 (37)
Dementia	44 (28)	25 (32)
Diabetes	29 (18)	18 (23)
Kidney failure	3 (2)	2 (3)

*Within-group valid percentages are shown.
POCT, point-of-care testing.

the duration of the trial, including a run-in period. A selected group of nurses and/or physicians was trained by POC experts of the diagnostic centre in the use of the device. The research team provided a medical training for the physicians on patient selection for CRP POCT and interpretation of CRP POCT results. Because of the pragmatic nature of the trial, decisions regarding the utilisation and interpretation of CRP POCT remained to the discretion of the physician during the trial.

Outcome measures

Effect outcome measures

The primary outcome was antibiotic prescribing (yes/no) at initial consultation, as registered by the physician. The secondary outcome was full recovery of the resident according to the treating physician (yes/no, ie, deceased or not fully recovered) at the end of the individual follow-up period, that is, 3 weeks after initial consultation. These effect outcomes were derived from the eCRFs.

Cost outcome measures

This economic evaluation was conducted from a healthcare perspective. Healthcare utilisation was assessed using the eCRFs and included antibiotic treatment (during follow-up), diagnostic utilisation and hospital stay (at baseline and follow-up). Costs of antibiotic use were calculated based on type and associated treatment duration as per guideline recommendations. Standard options in the eCRF for diagnostic tools that were used comprised sputum culture, CRP POCT, CRP via laboratory assessment and in-hospital thoracic imaging. For CRP via laboratory assessment we assumed that CRP was part of a standard blood test, and we also included diagnostics that were mentioned in the comment section for 'other diagnostics' (see online supplemental table S1). For each hospitalisation, the admission and return dates were collected to calculate length of stay.

Table 2 Multiply imputed effects and costs for POCT-guided care (n=162) and usual care (n=79)

Outcomes	POCT-guided care Mean (SE)	Usual care	Mean difference (95% CI)*
Avoided antibiotic prescription	0.47 (0.04)	0.18 (0.04)	0.30 (0.17 to 0.42)
Full recovery	0.86 (0.03)	0.91 (0.03)	–0.05 (–0.14 to 0.05)
Healthcare costs (€)			
Intervention (acquisition)	10 (0.41)	0 (0)	10 (10 to 11)
Intervention (in lease)	17 (0.68)	0 (0)	17 (16 to 19)
Intervention (frequent use)	9 (0.34)	0 (0)	9 (8 to 9)
Diagnostics	42 (11)	26 (5)	17 (–3 to 47)
Antibiotics	3 (0.87)	2 (1)	1 (–2 to 3)
Hospital admission	241 (89)	237 (107)	4 (–288 to 258)
Total costs (acquisition)	296 (90)	265 (110)	32 (–261 to 291)
Total costs (in lease)	303 (90)	265 (110)	39 (–262 to 299)
Total costs (frequent use)	295 (90)	265 (110)	30 (–267 to 291)

Multiple imputation model consisted of variables that differed at baseline, were related to missing data or were associated with the outcome: sex, severity of disease (subjective clinical judgement), congestive heart failure, tachypnoea, chronic obstructive pulmonary disease, a priori antibiotic prescribing (at the nursing home level) and unilateral abnormal lung sounds. The imputation procedure was stratified for treatment arm and cluster indicator variables were added to the imputation model to adjust for clustering in the imputation procedure.
*Uncertainty around cost differences estimated using the non-parametric bootstrap (bias-corrected and accelerated intervals).

Table 3 Results of the cost-effectiveness analyses and sensitivity analyses

Outcome*	ΔC (95% CI)†	ΔE (95% CI)	ICER	CE plane			
				NE	SE	SW	NW
Main analysis: Healthcare perspective							
Avoided antibiotic prescription	36 (–240 to 300)	0.26 (0.15 to 0.38)	137	60%	40%	0%	0%
Full recovery	36 (–240 to 300)	–0.06 (–0.16 to 0.03)	–579	2%	3%	36%	59%
SA1: Leasing the POCT							
Avoided antibiotic prescription	43 (–232 to 307)	0.26 (0.15 to 0.38)	163	63%	37%	0%	0%
Full recovery	43 (–232 to 307)	–0.06 (–0.16 to 0.03)	–691	2%	3%	34%	61%
SA2: Higher frequency of POCT use							
Avoided antibiotic prescription	34 (–241 to 298)	0.26 (0.15 to 0.38)	130	60%	40%	0%	0%
Full recovery	34 (–241 to 298)	–0.06 (–0.16 to 0.03)	–550	2%	3%	37%	58%
SA3: Complete-case analysis							
Avoided antibiotic prescription	76 (–276 to 425)	0.29 (0.16 to 0.41)	267	85%	15%	0%	0%
Full recovery	98 (–241 to 433)	–0.04 (–0.13 to 0.07)	–2431	54%	4%	11%	31%
SA4: Unadjusted analysis							
Avoided antibiotic prescription	36 (–240 to 300)	0.31 (0.21 to 0.42)	116	60%	40%	0%	0%
Full recovery	36 (–240 to 300)	–0.05 (–0.13 to 0.03)	–723	2%	4%	36%	58%
SA5: Ignore clustering							
Avoided antibiotic prescription	32 (–255 to 291)	0.26 (0.14 to 0.38)	121	60%	40%	0%	0%
Full recovery	32 (–255 to 291)	–0.06 (–0.16 to 0.03)	–505	4%	5%	35%	56%

*SA, sensitivity analysis.
†Uncertainty around cost differences estimated using the non-parametric bootstrap (bias-corrected intervals).
CE plane, cost-effectiveness plane; ICER, incremental cost-effectiveness ratio; NE, northeast quadrant; NW, northwest quadrant; POCT, point-of-care testing; SA, sensitivity analysis; SE, southeast quadrant; SW, southwest quadrant.

Costs of antibiotic treatment were valued using prices from an online database of the Dutch National Health Care Institute (online supplemental table S2).[31] Costs of diagnostics, other than CRP POCT, were valued based on available price lists of primary care laboratories that correspond to national tariffs. If appropriate, an additional fee was included for the sample collection or submission to the primary care laboratory. Valuation of hospital stay was based on standard costs (ie, average cost price per day) from the Dutch costing guideline.[32] Online supplemental table S1 specifies the reference source for each cost type. All costs were expressed in Euros for the year 2018. If necessary, costs were adjusted to 2018 using consumer price indices.[33]

The intervention costs were estimated using a bottom-up micro-costing approach and included costs of test materials, transport costs for these materials and depreciation costs for the CRP POC device. The annual depreciation costs were based on the average purchase price of the device using an expected 5-year product lifetime and divided by the average use of the device per year (UPCARE trial data: on average 39 times per device in the year 2019). We assumed that the CRP POC device was bought directly from a medical supplier. We calculated device cost based on the average of value added tax-free prices available online from Dutch medical suppliers (online supplemental table S3).

Statistical analysis

Missing data

The cost-effectiveness analyses and ROI analysis were conducted according to the intention-to-treat principle. Missing data were imputed using multiple imputation with chained equations (MICE).[34–37] Cost and effect data were assumed to be missing at random (MAR), which means that missing observations are explained by observed variables.[35 38] The imputation model included outcome variables and predictor variables that either differed at baseline, were related to missing data or were associated with the outcome, as well as variables included in the analysis model. To account for the skewed distribution of cost data, predictive mean matching was used in MICE.[37] The number of imputed data sets was increased until the loss of efficiency was less than 5%, resulting in five imputed data sets.[37] Each of the imputed data sets was analysed separately as described below. Results from the multiple data sets were pooled using Rubin's rules.[36]

Cost-effectiveness analysis

Multilevel regression models were used to estimate incremental costs and effects between the treatment groups, while accounting for the clustering of the data by allowing the intercepts to vary across clusters (ie, random intercepts model).[39 40] A two-level structure of the model was used including treating physicians and participants.

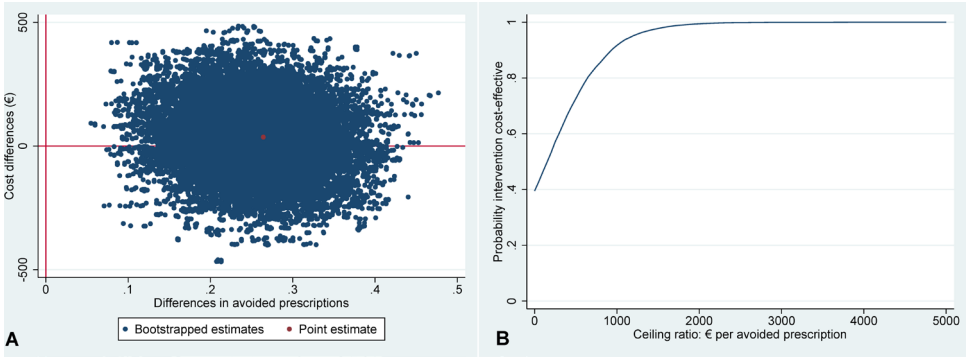

Figure 1 Cost-effectiveness plane (A) and cost-effectiveness acceptability curve (B) for antibiotic prescriptions at baseline.

The outcomes antibiotic prescribing and full recovery were additionally adjusted for baseline characteristics (see table 1 for descriptive statistics, and the legend of table 2 for the specific list of characteristics). For the cost-effectiveness outcomes, the difference in antibiotic prescription rate was multiplied by −1 to represent costs per antibiotic prescription avoided. Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the incremental costs by incremental effects. Bias-corrected bootstrapping stratified per nursing home was used to estimate statistical uncertainty (5000 replications). Statistical uncertainty surrounding ICERs was illustrated by plotting the bootstrapped cost-effect pairs on a cost-effectiveness plane (CE plane). Cost-effectiveness acceptability curves (CEACs) were also estimated, which present the probability that POCT-guided care is cost-effective compared with usual care for a range of different ceiling ratios (ie, the maximum willingness-to-pay threshold for one unit of effect extra).[41] For outcome measures such as antibiotic prescribing and full recovery, there is no consensus about what maximum willingness-to-pay would be acceptable.

Return-on-investment analyses

ROI analyses included intervention costs, which were similar to the cost-effectiveness analysis, and benefits related to the primary outcome measure, that is, the total costs of antibiotic prescriptions. Three ROI metrics were calculated: Net Benefits (NB: amount of money gained after costs are recovered), Benefit-Cost-Ratio (BCR: amount of money returned per Euro invested) and Return-On-Investment (ROI: percentage of profit per Euro invested).[42]

Multilevel regression models were used to estimate costs and benefits.[39 40] Bias-corrected and accelerated bootstrapping was used to estimate statistical uncertainty (5000 replications). The probability of financial return was estimated by determining the proportion of positive bootstrapped ROI metrics (ie, NB>0, BCR>1, ROI>0%).[42] Analyses were performed in IBM SPSS Statistics V.26 (IBM Corp, Armonk, New York, USA) and Stata/SE V.16 (StataCorp LP, College Station, Texas, USA).

Sensitivity analyses

To check the robustness of the results, five sensitivity analyses were performed. In the first sensitivity analysis, we assumed that the nursing home opted for a service partnership with a primary care laboratory (SA1). In this scenario, intervention costs comprised a service fee and costs per measurement, which includes transport costs. The yearly service fee covered lease-lending of the device, technical support, quality control and instructions and training of personnel working with the device. The service fee was divided by the average use of the device per year (39 times). In the second sensitivity analysis, we assumed higher frequency of POC device utilisation for the calculation of intervention costs (SA2). To this end, we only used the average of locations that used the device 20 times or more in the year 2019 (ie, 54 times/device). Furthermore, we performed a number of sensitivity analyses in which the statistical approach was changed, in order to assess methodological uncertainty. To assess the

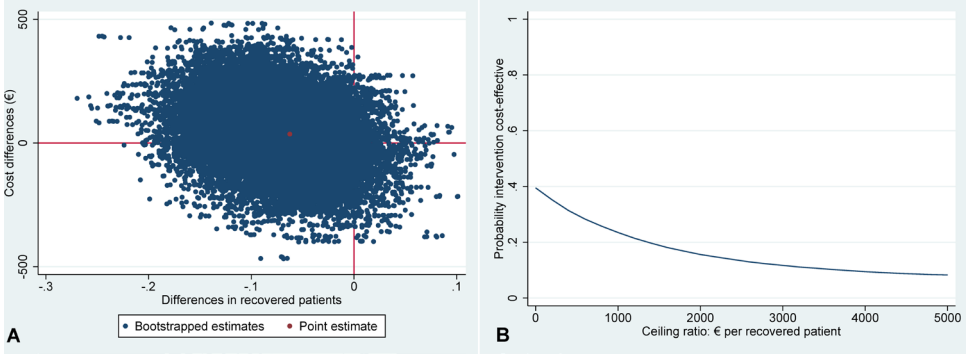

Figure 2 Cost-effectiveness plane (A) and cost-effectiveness acceptability curve (B) for full recovery at 3 weeks.

Table 4 Intervention costs, benefits, Net Benefits (NB), Benefit-Cost-Ratio (BCR) and Return-on-Investment (ROI) per patient

	Costs	Benefits			
	€	Total	NB	BCR	ROI
Main analysis	10.35 (9.71 to 11.04)	11.23 (6.00 to 16.60)	0.88 (–4.21 to 6.42)	1.09 (0.60 to 1.63)	8.54 (–40.44 to 62.84)

impact of missing data, we included an economic evaluation based on complete cases only (SA3). To assess the impact of confounders on cost-effectiveness outcomes, we also included a crude analysis; that is, without correction for confounders for the effect outcomes (SA4). Finally, the clustered nature of data was ignored in the estimation of incremental costs and effects (SA5).

RESULTS

Study population

We previously described demographics and baseline characteristics of UPCARE trial participants in more detail.[26] In summary, the group of POCT-guided care included 162 patients and the group of usual care included 79 patients with suspected LRTI. Baseline characteristics are shown in table 1. Most common comorbid conditions were chronic obstructive pulmonary disease (COPD), dementia and congestive heart failure. Baseline eCRFs were missing for three participants, and additionally data were missing for two participants for the outcome antibiotic prescribing at baseline and for 25 participants for the outcome full recovery at 3 weeks. Cost data were complete for 216 participants regarding diagnostics (total period), for 233 participants regarding changes in antibiotic management (follow-up period), and for 241 participants regarding hospital admission (total period).

Costs

For 139 participants (87.4%) in POCT-guided care, CRP POCT was used at initial consultation, and for 9 and 6 participants at 1 week and 3 weeks, respectively (data not shown). Table 2 shows that the mean intervention cost, that is, as used for the base-case analysis, was €10. The main cost driver of healthcare costs was the use of diagnostic resources (mean difference €17, 95% CI –3 to 47). However, there were no statistically significant differences in costs between POCT-guided care and usual care for any of the subcategories of healthcare costs. The difference in total healthcare costs between POCT-guided care and usual care was €32 per person (95% CI –261 to 291) for the base-case scenario.

Clinical outcomes

The proportion of patients with suspected LRTI who did not receive antibiotics at baseline was 0.47 (SE 0.04) in POCT-guided care and 0.18 (SE 0.04) in usual care (see table 2). The mean difference in prescribing rates between groups was 0.30 (95% CI 0.17 to 0.42). The full recovery rate at the end of the follow-up period was 0.86 in POCT-guided care and 0.91 in usual care (mean difference –0.05, 95% CI –0.14 to 0.05).

Cost-effectiveness analyses

Table 3 shows the results of the cost-effectiveness analyses. The ICER for the outcome antibiotic prescribing was €137 per avoided antibiotic prescription. The CE-plane in figure 1A and table 3 shows that 60% of the bootstrapped cost-effect pairs were located in the northeast quadrant (ie, POCT-guided care was more expensive and more effective compared with usual care) and 40% were located in the southeast quadrant (ie, POCT-guided care was less expensive and more effective than usual care). The CEAC in figure 1B shows that the probability of CRP POCT being cost-effective compared with usual care is 0.40, 0.80 and 0.92 when the ceiling ratio was set at €0, €650 and €1000 per antibiotic prescription avoided.

The CE-plane for full recovery in figure 2A shows that the majority of bootstrapped cost-effect pairs was located in the northwest quadrant (ie, POCT-guided care was more expensive and less effective than usual care). The ICER for the secondary outcome full recovery at 3 weeks was €–579, which means that the full recovery of one patient less was associated with an investment of €579 in POCT-guided care compared with usual care. The CEAC in figure 2B shows that the probability of CRP POCT being cost-effective compared with usual care is 0.40, 0.24 and 0.16 when the ceiling ratio was set at €0, €1000 and €2000, respectively, per additionally recovered patient.

Return-on-investment

Table 4 shows that during follow-up, intervention costs amounted to €10.35 and total benefits in terms of avoided antibiotic prescriptions were €11.23 per patient (95% CI 6.00 to 16.60). The NB was on average 0.88 (95% CI –4.21 to 6.42), the BCR was 1.09 (95% CI 0.60 to 1.63) and the ROI was 8.54% (95% CI –40.44 to 62.84), respectively. The proportion of bootstrapped replications that resulted in an NB>0, BCR>1 and ROI>0%, that is, the probability of financial return, was 0.65. Overall, these findings indicate that POCT-guided care is associated with a statistically non-significant minor net profit for the nursing homes.

Sensitivity and scenario analyses

Table 2 shows that the mean intervention cost reduced to €9 in the scenario that the CRP analyser was used more frequently (54 times/device/year). The mean intervention cost was €17 in the scenario that CRP devices were leased via service partnership instead of being bought directly from a medical supplier. In the different sensitivity

analyses (SA) for antibiotic prescribing (table 3), ICERs ranged between €116 and €267 per avoided antibiotic prescription. ICERs for antibiotic prescribing were robust in most sensitivity analyses, with the largest impact resulting from a different financing method for CRP POCT (SA1) and handling missing data (SA3). For full recovery, ICERs ranged from €−505 to €−2431 per additional full recovery of one patient. ICERs were most affected by adjustment for missing data and baseline characteristics, that is, SA3 and SA4.

DISCUSSION

Main findings

This study evaluated the cost-effectiveness and ROI of POCT-guided care compared with usual care for nursing home residents with suspected LRTI. Significantly less antibiotics were prescribed in POCT-guided care compared with usual care. Total costs in POCT-guided care were higher than in usual care, and recovery rates lower, but these differences between groups were small and not statistically significant. POCT-guided care was associated with a cost of €137 per antibiotic prescription avoided, and cost per fully recovered patient less was €579 compared with usual care. The probability of CRP POCT being cost-effective at a willingness-to-pay threshold of €0 per antibiotic prescription avoided was 40% and this increased to 80% at a threshold of €650 per antibiotic prescription avoided. The ROI results showed that the investment for CRP POCT resulted in a minor, statistically non-significant profit for the nursing home due to reduced cost of antibiotic prescriptions.

Strengths and limitations

A strength of the current economic evaluation is the pragmatic design of the trial. This means that actual practice is resembled as much as possible, which increases generalisability of the results. In the methods section we describe the Dutch nursing home setting to allow for comparison of this setting within different countries. Furthermore, we accounted for clustering at the physician level in the analyses, which is frequently ignored in cost-effectiveness analyses alongside cluster-randomised trials.[39 43–45] Differences in physician preferences regarding management decisions might have an impact on both costs and effects. However, dealing with clustering versus ignoring clustering at the physician level had a limited impact on the point estimates in the current study. Furthermore, we used the same analysis model (ie, same outcome measures and with correction for clustering and baseline characteristics) in the effectiveness analysis and the current cost-effectiveness analyses to minimise differences in outcomes. With the correction for baseline characteristics we aimed to address potential baseline imbalances.[26] However, the unadjusted sensitivity analysis showed that omitting baseline characteristics had a minor impact on the ICER estimation for the outcome antibiotic prescribing at baseline. Finally, missing data were dealt with using multiple imputation, which is the preferred method for imputing variables with missing data.[46] Also, sensitivity analyses showed that not dealing with missing data increased ICER estimations to an important extent.

The current study also has a number of limitations. First, no preference-based quality of life measure has been used in the trial (eg, EuroQol questionnaire or Short-Form Six-Dimension (SF-6D)). As a consequence, no cost–utility analysis could be performed to compare the current intervention with alternative interventions across different disease areas. This also means that we cannot compare our results against the Dutch willingness-to-pay threshold which ranges between €20 000 and €80 000 per quality-adjusted life year.[47] Second, we used a healthcare perspective in the economic evaluation. Thus, we only included healthcare costs, which is different from a societal perspective in which all relevant costs are included regardless of who bears them. Consequently, we were not able to identify potential cost shifts between sectors, for instance from the healthcare system to the patient.[48] However, considering that patients were nursing home residents and do not work anymore, we expect that societal costs related to the patient are limited (eg, informal care and productivity losses). Also, the current study aims to inform decisions regarding implementation at the nursing home level, within context of the Dutch Long-Term Care Act which decentralises certain budget decisions to this setting. Third, we are unsure whether the assumption holds that data were MAR, because it is not possible to distinguish between MAR and Missing Not At Random (ie, missing data are related to the variable with missing observations itself). Recently, an increasing number of studies emphasise the importance of checking for possible departure from the MAR assumption.[35 49–52] To evaluate this, methods such as selection and/or pattern-mixture models are recommended, which we have not used in this study.[52] Lastly, the time horizon of the economic evaluation was short (ie, 3 weeks). Nonetheless, since our study was conducted in the nursing home setting, we anticipated that the most important and relevant health and cost outcomes directly related to the LRTI episode would occur within this period.

Comparison with other studies

The current findings are largely comparable to studies in primary care showing mostly higher costs and lower antibiotic prescribing in POCT-guided care compared with usual care for LRTI or acute exacerbations of COPD.[14 53–55] For instance, studies in primary care showed overall ICERs of €126 and €250 per 1% reduction in antibiotic prescribing in POCT-guided care compared with usual care, for LRTI and acute exacerbations of COPD, respectively.[14 54] Although hospitalisation often is considered as a main cost driver in nursing home settings for

suspected LRTI, hospital admission from a nursing home is generally uncommon in the Netherlands.[11 56 57] This is also reflected in our results which show that the main cost drivers were intervention costs and costs of other diagnostic resources, although the between-group difference in hospitalisation costs was small.

Meaning of the study

Currently, there are no commonly accepted willingness-to-pay thresholds for our study outcomes. Therefore, as a society we need to make a trade-off decision regarding which probability of cost-effectiveness and willingness-to-pay ratio are acceptable. Although there is no formal threshold, if we consider an 80% probability of cost-effectiveness sufficient in the current study, then CRP POCT can be considered cost-effective compared with usual care for suspected LRTI in nursing home residents if we, as a society, are willing to pay at least €650 per avoided antibiotic prescription. Potentially, costs of POCT-guided care may be reduced if future technological developments enable combined POCT for multiple biomarkers, and if laboratories purchase equipment on a larger scale for leasing purposes. Additionally, the higher cost associated with CRP POCT might be a worthwhile investment, because of reduced diagnostic uncertainty and better patient management in general.

When deciding about implementation of CRP POCT in practice, the setting of the current economic evaluation should be taken into consideration. Hospitalisation of nursing home residents is generally uncommon in the Netherlands.[30 57] Potentially, if POCT-guided care improves patient selection for hospital admission in other populations, this could improve potential cost-effectiveness of CRP POCT use in these settings. Furthermore, results of the current economic evaluation should be considered alongside evidence for effectiveness for any decision-making processes regarding implementation of CRP POCT in the nursing home. The development of antimicrobial resistance is an important point of consideration from a societal perspective regarding both health and costs.[58]

The current economic evaluation assessed full recovery at 3 weeks as a secondary outcome. However, the finding that CRP POCT is not cost-effective with regard to full recovery at 3 weeks should be interpreted cautiously, first, because of the small and statistically non-significant difference in full recovery at 3 weeks. Second, appropriate withholding of antibiotics may be associated with somewhat prolonged illness duration in these patients (eg, duration of cough), as could be the case with acute bronchitis.[53 59] In specific cases CRP POCT might contribute to short-term health benefits. For instance, early discrimination of acute decompensated heart failure from pneumonia could facilitate prompt management with, for example, diuretics.[60] Potential societal health and cost benefits related to possibly reduced antimicrobial resistance would be expected in the longer term, which were outside the scope of this study.[53]

Conclusion and future research

This economic evaluation shows that POCT-guided care in the nursing home setting effectively reduced antibiotic prescribing compared with usual care without significant effects on recovery rates, but, it requires an investment. For each avoided antibiotic prescription an additional €137 should be invested in POCT-guided care compared with usual care. Although the time horizon of the current study may be comprehensive enough to assess health and cost parameters directly associated with suspected LRTI, it could be valuable to extrapolate costs and consequences of CRP POCT compared with usual care without CRP POCT in a model-based economic evaluation with a life-time horizon (ie, until all participants are deceased). Such a model would be able to test the hypothesis that a pneumonia episode marks or precipitates a series of events leading up to mortality in the elderly population.[61] Furthermore, in the current economic evaluation we could not take into account future antibiotic resistance costs, which might impact the cost-effectiveness of CRP POCT use within a wider time span. Cost estimations in primary care settings might not be suitable for direct extrapolation to the nursing home setting.[62] Future studies could estimate such costs to improve future economic evaluations of interventions for rational antibiotic prescribing in this setting.

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