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# Tailored Interventions to Improve Antibiotic Use for Lower Respiratory Tract Infections in Hospitals: A Cluster-Randomized, Controlled Trial

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(See the editorial commentary by File and Gross on pages 942–4)

**Background.** Limited data exist on the most effective approach to increase the quality of antibiotic use for lower respiratory tract infections at hospitals.

**Methods.** One thousand nine hundred six patients with community-acquired pneumonia or an exacerbation of chronic obstructive pulmonary disease (acute exacerbation of chronic bronchitis) were included in a cluster-randomized, controlled trial at 6 medium-to-large Dutch hospitals. A multifaceted guideline-implementation strategy that was tailored to baseline performance and considered the barriers in the target group was used. Principal outcome measures were (1) guideline-adherent antibiotic prescription, (2) adaptation of dose and dose interval of antibiotics according to renal function, (3) switches in therapy, (4) streamlining of therapy, and (5) Gram staining and culture of sputum samples. Secondary process outcomes were applicable to community-acquired pneumonia (e.g., timely administration of antibiotics) or acute exacerbation of chronic bronchitis (e.g., not prescribing macrolides).

**Results.** The rate of guideline-adherent antibiotic prescription increased from 50.3% to 64.3% in the intervention hospitals (odds ratio [OR], 2.63; 95% confidence interval [CI], 1.57–4.42;  $P = .0008$ ). The rate of adaptation of antibiotic dose according to renal function increased from 79.4% to 95.1% in the intervention hospitals (OR, 7.32; 95% CI, 2.09–25.7;  $P = .02$ ). The switch from intravenous to oral therapy improved more in the control hospitals (from 53.3% to 71.9%) than in the intervention hospitals (from 74% to 83.6%). The change from broad-spectrum empirical therapy to pathogen-directed therapy improved by 5.7% in the intervention hospitals ( $P =$  not significant). Fewer sputum samples were obtained from both the intervention group (rate of sputum samples obtained decreased from 55.8% to 53.1%) and the control group (rate of sputum samples obtained decreased from 49.6% to 42.7%). Timely administration of antibiotics for community-acquired pneumonia increased significantly in the intervention group (from 55.2% to 62.9%; OR, 2.49; 95% CI, 1.11–5.57;  $P = .026$ ).

**Conclusions.** With regard to some important aspects, tailoring interventions to change antibiotic use improved the quality of treatment for patients hospitalized with lower respiratory tract infection.

Improvement of the quality of antibiotic use for hospitalized patients with lower respiratory tract infection (LRTI)—for example, by means of the timely administration of antibiotics and ensuring the appropriate

selection of the initial antibiotic regimen—is related to better patient outcomes [1, 2]. Inappropriate use of antibiotics contributes to the emergence and spread of drug-resistant microorganisms, as well as to increased treatment costs [3]. International guidelines provide recommendations for the initial evaluation and treatment of LRTI and include advice about judicious antibiotic therapy [4–7]. However, studies have shown a wide variation of adherence to these guidelines in daily practice [8].

A systematic review of studies of the improvement of management of community-acquired pneumonia (CAP) reported various strategies that can improve ad-

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herence to guidelines [9]. The most methodologically robust study showed that the implementation of a critical-care pathway is effective for reducing institutional resources, but it did not assess the actual performance of processes of treatment and showed no reduction in intensive care unit admission, readmission, or mortality rate [2]. Other studies have had a more limited scope [10, 11] or did not control for secular trends [12, 13]. Thus, there is still a lack of research with regard to the best approach to improve antibiotic use in hospitals.

Theories of effective change suggest that choosing potentially effective intervention strategies is important and that interventions should be tailored to the performance aspects most in need of improvement; it is futile to invest in aspects for which performance is already optimal. In addition, the choice of intervention should be made on the basis of the assessment of potential barriers to performance change for the target group and context [14, 15]. To our knowledge, no specific studies to improve in-hospital antibiotic treatment of patients with acute exacerbations of chronic bronchitis (AECB) or chronic obstructive pulmonary disease have been published.

Therefore, we performed a cluster-randomized, controlled trial at 6 hospitals; the aim was to improve the antibiotic treatment of patients with CAP or AECB. We used an intervention strategy that targeted the aspects most in need of improvement (as indicated by the preintervention baseline performance) and considered the barriers to appropriate antibiotic use.

## PATIENTS AND METHODS

### Study Design

We performed a multicenter, cluster-randomized trial to assess the effectiveness of a multifaceted implementation strategy to improve the quality of antibiotic use for LRTI. Six medium-to-large hospitals in the southeast of The Netherlands took part in this study. The trial was registered with ClinicalTrials.gov (identifier, NCT00129883). The regional research ethics committee approved our study and waived the need for informed, written consent from the patients. Measures were taken to protect patient privacy. Randomization took place at the hospital level, but our intervention was delivered both at the hospital level and at the professional level. To reduce chance imbalances, we pair-matched the clusters for important variables, including teaching status, hospital size, and mean outcomes for key indicators in our baseline study. R.P.A., who was blinded to the composition of the groups, flipped a coin to determine which hospitals would be in the intervention and control groups.

### Patients

We prospectively enrolled patients who were admitted to our 6 participating hospitals during 1 September 2002–1 March 2003 and 1 September 2004–1 March 2005. Eligible patients with CAP met 3 of the following inclusion criteria: (1) age of

$\geq 18$  years, (2) evidence of an infiltrate on the chest radiograph (as determined by the admitting professional or an onsite radiologist) and  $\geq 2$  of 6 clinical criteria for CAP (cough, colored sputum, temperature  $>38.5^{\circ}\text{C}$ , abnormal chest auscultation, WBC count  $>10 \times 10^9$  cells/L or  $<4 \times 10^9$  cells/L, or positive blood or pleural fluid culture result), and (3) a clinical diagnosis of pneumonia that was established by the managing professional during hospitalization.

Eligible patients with AECB fulfilled the following inclusion criteria: (1) age of  $\geq 18$  years; (2) recent increase in dyspnea, sputum production, and/or change of aspect of sputum (at least 2 of these 3 criteria); (3) a clinical diagnosis of AECB that was established by the managing professional; and (4) the absence of a new radiographic infiltrate (as determined by the admitting professional or an onsite radiologist).

We excluded the following patients: (1) patients who lived in nursing homes, (2) patients who had underlying immunodeficiency (HIV infection, neutropenia, receipt of treatment with immunomodulating drugs, active hematological malignancies, anatomical or functional asplenia, and hypogammaglobulinemia), (3) patients who were treated with antibiotics for another culture-proven infection during the time of admission to the hospital, (4) patients who had LRTI and were discharged from the hospital during the preceding 30 days, (5) patients who were transferred to another hospital or intensive care unit or who died within 24 h of admission, and (6) patients who had a very poor prognosis and who were admitted for palliative care (i.e., they had a life expectancy of  $<2$  weeks).

### Variables

**Process-of-care measures.** Using a formal procedure, we selected 15 indicators from key guideline recommendations (9 indicators for CAP and 6 for AECB) for the appropriate use of antibiotics for LRTI on the basis of national and international guidelines and a systematic review of the literature [16–19]. Five indicators were applicable to both AECB and CAP (tables 1 and 2). A sum score was calculated that determined the percentage of patients who received all applicable quality indicators (all-or-none measurement) [20]. Four additional indicators were applicable only for CAP, and 2 were applicable only for AECB (tables 3 and 4).

**Patient outcome measures.** We collected secondary outcome measures, including duration of hospital stay, all-cause in-hospital mortality, and intensive care unit admission for hemodynamic compromise or respiratory failure.

### Study Intervention

**Analysis of barriers to implementation.** Prior to our study, we conducted a qualitative study to understand the barriers to appropriate antibiotic use for patients with LRTI [21]. This study suggested that different recommendations for the use of

**Table 1. Performance of quality indicators before and after intervention of treatment protocols for patients with lower respiratory tract infection (by patient analysis).**

Quality indicator	Intervention group		Control group		OR <sup>a</sup> (95% CI)	P	Corrected OR <sup>b</sup> (95% CI)	P
	Before (n = 421)	After (n = 508)	Before (n = 359)	After (n = 363)				
Empirical antibiotic regimen at correct indication and according to guidelines	187/372 (50.3)	296/460 (64.3)	175/326 (53.7)	154/338 (45.6)	2.34 (1.43–3.83)	.0008	2.63 (1.57–4.42)	.0003
Adapting dose and dose interval of antibiotics according to renal function	201/253 (79.5)	310/326 (95.1)	273/285 (95.8)	231/250 (92.4)	7.32 (2.09–25.7)	.002	12.9 (3.64–45.8)	<.0001
Switching from intravenous to oral therapy, according to existing criteria	142/192 (74)	199/238 (83.6)	120/225 (53.3)	138/192 (71.9)	1.75 (0.10–30.21)	.486	1.20 (0.02–76.51)	.931
Changing broad-spectrum, empirical therapy to pathogen-directed therapy (streamlining therapy)	80/111 (72.1)	77/99 (77.8)	47/71 (66.2)	28/49 (57.1)	1.88 (0.32–11.03)	.456	1.94 (0.34–11.03)	.456
Obtaining sputum samples for Gram staining and culture	235/421 (55.8)	270/508 (53.2)	178/359 (49.6)	155/363 (42.7)	1.03 (0.59–1.83)	.908	1.13 (0.64–2.00)	.672
Sum score <sup>c</sup>	22.1	29.1	18.7	15.7	1.77 (0.94–3.34)	.079	...	

**NOTE.** Data are proportion of patients (%), unless otherwise indicated.

<sup>a</sup> ORs were adjusted for clustering of patients relative to professionals and hospitals in a multilevel analysis.

<sup>b</sup> ORs were corrected for potential patient, professional, and hospital confounding factors [23].

<sup>c</sup> Percentage of patients for whom all 5 key quality indicators for LRTI were performed (all-or-none measurement).

**Table 2. Performance of quality indicators before and after intervention of treatment protocols for patients with lower respiratory tract infection per hospital (by patient analysis).**

Quality indicator	Intervention hospitals						Control hospitals					
	1		2		3		4		5		6	
	Before (n = 177)	After (n = 193)	Before (n = 154)	After (n = 216)	Before (n = 90)	After (n = 99)	Before (n = 137)	After (n = 125)	Before (n = 126)	After (n = 115)	Before (n = 96)	After (n = 117)
Empirical antibiotic regimen at correct indication and adherent to national guidelines	70/151 (46.4)	97/165 (58.8)	63/139 (49.6)	133/204 (65.2)	48/82 (58.5)	66/91 (72.5)	74/123 (60.2)	58/120 (48.3)	55/112 (49.1)	43/110 (39.1)	46/91 (50.5)	53/108 (49.1)
Adapting dose and dose interval of antibiotics according to renal function	100/114 (87.8)	137/141 (97.2)	66/90 (73.3)	132/143 (92.3)	35/49 (71.4)	41/42 (97.6)	106/112 (94.6)	94/94 (100)	96/102 (94)	82/99 (82.8)	71/71 (100)	55/57 (96.5)
Switching from intravenous to oral therapy, according to existing criteria and when clinically stable	53/68 (77.9)	57/63 (90.5)	36/56 (64.3)	86/117 (73.5)	53/68 (77.9)	61/66 (92.4)	21/96 (21.9)	34/64 (53.1)	62/66 (93.9)	61/68 (89.7)	37/63 (58.7)	41/57 (71.9)
Changing broad-spectrum empirical therapy to pathogen-directed therapy (streamlining therapy)	40/60 (66.7)	39/53 (73.6)	22/23 (95.6)	29/34 (85.3)	18/28 (64.3)	9/12 (75)	19/25 (76)	6/13 (46.2)	18/27 (81.8)	15/23 (65.2)	15/24 (62.5)	7/13 (53.8)
Obtaining sputum samples for Gram staining and culture	99/177 (55.9)	120/193 (62.2)	77/154 (50.0)	112/216 (51.9)	59/90 (65.5)	59/99 (59.6)	64/137 (46.7)	34/125 (27.2)	77/126 (61.1)	75/115 (65.2)	37/96 (38.5)	46/117 (39.3)

**NOTE.** Data are proportion of patients (%).

**Table 3. Performance of additional quality indicators before and after intervention of treatment protocols for patients with community-acquired pneumonia (by patient analysis).**

Quality indicator	Intervention group			Control group			OR <sup>a</sup> (95% CI)	P	Corrected OR <sup>b</sup> (95% CI)	P
	Before (n = 212)	After (n = 276)	Change, %	Before (n = 166)	After (n = 173)	Change, %				
Timely initiation of antibiotic therapy (within 4 h after presentation)	80/145 (55.2)	105/167 (62.9)	+7.7	66/97 (68)	33/64 (51.6)	-16.4	2.49 (1.11–5.57)	.0269	3.59 (1.02–12.6)	.046
Stopping antibiotic therapy after 3 consecutive days of defervescence	5/147 (3.4)	33/193 (17.1)	+13.7	19/125 (15.2)	9/120 (7.5)	-7.7	13.86 (3.9–49.4)	.0001	NA <sup>c</sup>	
Obtaining 2 sets of blood samples for culture	112/212 (52.8)	167/276 (60.5)	+7.7	97/166 (58.4)	94/173 (54.3)	-4.1	1.60 (0.83–3.07)	.1545	1.65 (0.75–3.69)	.20
Urine antigen testing for <i>Legionella</i> species because of clinical suspicion	11/14 (78.6)	20/24 (83.3)	+4.7	12/16 (75.0)	12/13 (92.3)	+17.3	0.34 (0.02–6.56)	.4823	NA <sup>c</sup>	

**NOTE.** Data are proportion of patients (%), unless otherwise indicated. NA, not applicable.

<sup>a</sup> ORs were adjusted for clustering of patients relative to professionals and hospitals in a multilevel analysis.

<sup>b</sup> ORs were corrected for potential patient, professional, and hospital confounding factors.

<sup>c</sup> No additional confounding factors tested [23].

an antibiotic have different barriers that must be overcome, and different types of intervention are required. An example that describes how the assessment of barriers leads to a “targeted” intervention is provided in the Appendix. As such, we designed interventions for each particular recommendation (figure 1). Our intervention strategy comprised both fixed and flexible phases.

**Phase I.** During the first, fixed phase of our intervention, intervention hospitals (IHs) installed a local organizing committee. In each hospital, a clinical pharmacist, a medical microbiologist, a physician, a pulmonologist, and a quality-improvement officer participated. A key lecture was given in each IH by a respected opinion leader during a kick-off meeting. Feedback on indicator performance at the hospital level was presented and provided in writing to all doctors treating hospital LRTIs. Feedback reports included benchmarks at the hospital level (best practice) and presented key issues for improvement. Consensus “critical-care pathways” were distributed to all doctors as a laminated, pocket card; desktop and personal digital assistant versions were also distributed.

**Phase II.** During the flexible phase (phase II), the components of intervention were adjusted to the needs and wishes of every single IH. Local hospital baseline study results were discussed during local organizing committee meetings. The indicators that were most in need of improvement were given priority in the intervention protocol. The elements for intervention were selected on the basis of analysis of the barriers that were specific to each key guideline recommendation. These interventions were implemented in 3 modules, including initiation of therapy, change of therapy, and diagnostic procedures (figure 1). Local processes of treatment were analyzed, and work processes were redesigned. Our external quality facilitator initiated and coordinated this intervention.

#### Data Collection

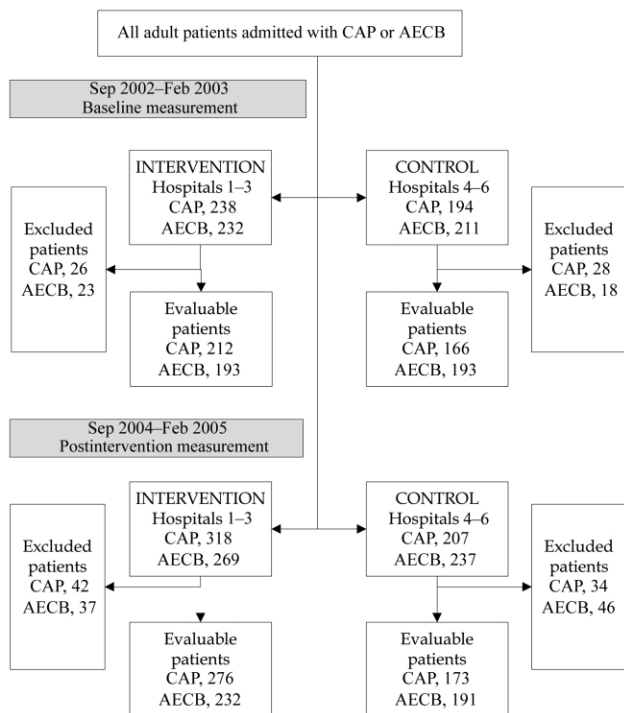
All data were collected by concurrent chart review; trained research assistants made twice-weekly reviews of the charts of all patients who were admitted to the internal and respiratory medicine wards. Patient characteristics included demographic

**Table 4. Performance of additional quality indicators before and after intervention of treatment protocols for patients with acute exacerbation of chronic bronchitis (AECB) or chronic obstructive pulmonary disease (COPD; by patient analysis).**

Quality indicators for AECB	Intervention group			Control group			OR <sup>a</sup> (95% CI)	P
	Before (n = 209)	After (n = 193)	Change, %	Before (n = 232)	After (n = 191)	Change, %		
Macrolide therapy not first choice treatment for bronchitis in exacerbations of COPD	104/105 (99)	135/141 (95.7)	-3.3	139/148 (93.9)	115/129 (89.1)	-4.8	0.53 (0.06–5.10)	.589
Optimal duration of antibiotic therapy from 5 to 7 days	24/93 (25.8)	47/127 (37.0)	+11.2	73/141 (51.8)	51/119 (42.9)	-8.9	2.22 (0.96–5.12)	.062

**NOTE.** Data are proportion of patients (%), unless otherwise indicated.

<sup>a</sup> ORs were adjusted for clustering of patients relative to professionals and hospitals in a multilevel analysis.



**Figure 1.** Flowchart of hospitals and patients

data, comorbidity data, findings from a physical examination that was performed during admission, and initial laboratory and radiology results (tables 5 and 6). Data collection was validated at regular intervals; 2 independent researchers performed double-chart reviews for 10% of the patients. These researchers agreed on indicator level, which was corrected for chance and expressed in  $\kappa$  coefficients, with a range of 0.7–1 (good to very good).

Care-provider characteristics were collected from questionnaires that were completed by all specialists at our study hospitals. Hospital characteristics were obtained from a national survey (table 7) [22].

### Statistical Analysis

Descriptive statistics included frequencies, percentages, means, medians, and SDs. Hospital, professional, and patient characteristics of study hospitals were compared with Student's *t* test and a nonparametric test (Mann-Whitney *U* test) for continuous variables and a  $\chi^2$  analysis for proportions.  $P < .05$  was considered to be statistically significant. We performed a multilevel logistic analysis to assess effectiveness, adjusting for clustering of patients and professionals in hospitals. We calculated the intraclass correlation coefficients to rate the degree of clustering. We constructed the generalized estimating equation models with a Glimmix procedure, using SAS statistical software, version 8.2 for Windows (SAS Institute). For each indicator outcome, the basic model included effects on the in-

tervention group versus the control group and on the timing of measurement (preintervention vs. postintervention). The model also included the interaction between these 2 variables. For each specific indicator, results were adjusted for patient, professional, and hospital factors that independently predicted indicator performance [23]. The adjusted estimates and their associated SEs were converted to ORs with 95% CIs.

## RESULTS

### Study Population

At baseline, our intervention group consisted of 470 patients (238 patients with CAP and 232 patients with AECB), and our control group consisted of 405 patients (194 patients with CAP and 211 patients with AECB). The postintervention groups included 587 intervention patients and 444 control patients (figure 2). Exclusion rates varied from 10.4% to 17.8%, and exclusions were mainly attributable to the recent discharge (within 30 days) of patients with LRTI (tables 5 and 6).

No clinically relevant differences were detected for characteristics of hospitals and professionals between our IHs and CHs at baseline (table 7). Fewer patients with chronic obstructive pulmonary disease were included in our CAP control group at baseline than in the intervention group (table 5). This was because the patient inclusion rate was higher in the general internal medicine wards than in the respiratory units of our CHs at baseline. This may have led to an uneven distribution of patients with chronic heart failure (46.2% vs. 27.7%;  $P < .01$ ) and of patients with  $>1$  comorbidity (44.8% vs. 33.7%;  $P = .03$ ).

### Effects

Table 1 shows the pre- and postintervention performance of 5 quality indicators and a sum score. Table 2 shows the outcomes per hospital. Performance improved statistically significantly for 2 of 5 indicators in our IHs, compared with the CHs.

#### Guideline adherence for empirical antibiotic therapy.

The rate of adherence to guidelines for empirical therapy increased from 50.3% to 64.3% in the IHs (OR, 2.63; 95% CI, 1.57–4.42). Improvement was equally distributed among the 3 IHs (increases of 12.4%, 15.6%, and 14.0%). However, in hospital 1, this was predominantly because of an improvement in the administration of antibiotics at the correct indication for AECB (from 29.1% to 51.5%), rather than because of the prescription of antibiotics according to the CAP guideline (from 56.3% to 63.9%). In hospital 2, empirical prescription for both AECB and CAP improved, and in hospital 3, all improvement was because of better adherence to recommendations for the treatment of CAP (from 39.5% to 53.3%).

**Adapting the dose and dose interval in the presence of decreased renal function.** At baseline, there was a significant difference between adherence to the adaptation of the dose and

**Table 5. Patient characteristics before and after intervention of treatment protocols for patients with community-acquired pneumonia.**

Characteristic	Baseline cohort			Postintervention cohort		
	Intervention (n = 238)	Control (n = 194)	P	Intervention (n = 318)	Control (n = 207)	P
Evaluable patients	212	166	...	276	173	...
Male sex	124 (58.5)	93 (56)	.63 <sup>a</sup>	174 (63)	106 (61.3)	.71 <sup>a</sup>
Age, mean years ± SD	69.6 ± 16.2	70.8 ± 14.6	.47 <sup>b</sup>	68.7 ± 16.2	71.8 ± 16.4	.05 <sup>b</sup>
PSI score >3	99 (46.7)	78 (47)	.96 <sup>a</sup>	130 (47.4)	84 (48.8)	.78 <sup>a</sup>
Comorbidity score <sup>c</sup> >1	95 (44.8)	56 (33.7)	.03 <sup>a</sup>	94 (34.1)	75 (43.1)	.05 <sup>a</sup>
COPD	109 (51.4)	62 (37.3)	.01 <sup>a</sup>	129 (46.7)	91 (52.6)	.23 <sup>a</sup>
Chronic heart failure	98 (46.2)	46 (27.7)	<.01 <sup>a</sup>	84 (30.4)	36 (20.8)	.025 <sup>a</sup>
Confusion during presentation	17 (17.7)	15 (25.4)	.25 <sup>a</sup>	21 (12.8)	28 (17.4)	.25 <sup>a</sup>
Oxygen saturation, mean % ± SD	93 ± 4.5	91.9 ± 4.9	.06 <sup>b</sup>	93.3 ± 4.8	92.3 ± 4.5	.05 <sup>b</sup>
Temperature, mean °C ± SD	38.1 ± 1.1	37.9 ± 1.1	.01 <sup>b</sup>	38.2 ± 1.0	38.0 ± 1.1	.2 <sup>b</sup>
Pulse, mean beats/min ± SD	98.3 ± 19.6	94.8 ± 21.8	.12 <sup>b</sup>	98.1 ± 19.4	96.5 ± 20.8	.43 <sup>b</sup>
Sodium level, mean mmol/L ± SD	137.3 ± 4.1	135.5 ± 4.9	.01 <sup>b</sup>	136.6 ± 4.4	136.2 ± 4.1	.43 <sup>b</sup>
Antibiotic therapy within 30 days	70 (33.0)	49 (29.5)	.92 <sup>a</sup>	83 (30.0)	58 (33.5)	.32 <sup>a</sup>
Admission to respiratory unit	181 (87.4)	99 (59.6)	<.01 <sup>a</sup>	229 (83)	158 (91.3)	.012 <sup>a</sup>
Hospital mortality	13 (6.1)	15 (9.0)	.29 <sup>a</sup>	20 (7.2)	15 (8.7)	.58 <sup>a</sup>
ICU admission	5 (2.4)	7 (4.2)	.31 <sup>a</sup>	6 (2.2)	2 (1.2)	.43 <sup>a</sup>
Duration of stay, median days	10.0	12.0	.23 <sup>b</sup>	8.0	10.0	.47 <sup>b</sup>

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; PSI, pneumonia severity index.

<sup>a</sup> Determined by  $\chi^2$  test.

<sup>b</sup> Determined by Student's *t* test or Mann-Whitney *U* test.

<sup>c</sup> Sum score of 8 items, including malignancy, liver disease, chronic heart failure, stroke, renal failure, diabetes, alcohol abuse, and chronic lung disease.

dose interval in the presence of decreased renal function between the IHs and the CHs (79.4% vs. 95.8%). The rate of adherence to this indicator increased in our IHs (from 79.4% to 95.1%), and a ceiling effect occurred in the CHs (the rate decreased slightly from 95.8% to 92.4%).

**Switch therapy.** The switch from intravenous to oral therapy improved in our IHs (from 74% to 83.6%) and even more in our CHs (from 53.3% to 71.9%). The increase was most prominent in one of the control hospitals; hospital 4 had an increase of 31.2% (from 21.9% to 53.1%).

**Streamlining therapy.** The change from broad-spectrum provisional therapy to pathogen-directed therapy for LRTIs showed an overall 5.7% improvement in our IHs. In the CHs, performance decreased (from 66.2% to 57.1%). Streamlining therapy was only possible for a small number of patients. There were 111 such patients (26%) in the intervention group at baseline, and there were only 71 eligible patients (19.7%) in the control group. The increase in adherence for this indicator was not statistically significant (OR, 1.88; 95% CI, 0.32–11.03; *P* = .46).

**Performance of diagnostic procedures: sputum sample for Gram staining and culture.** Fewer sputum samples were obtained both from the intervention group (from 55.8% to 53.1%) and the control group (from 49.6% to 42.7%). Overall, there was a 7% increase of patients who received all recom-

mended processes of treatment in the intervention group (from 22.1% to 29.1%; OR, 1.77; 95% CI, 0.94–3.34; *P* = .079).

**Additional quality indicators for CAP and AECB.** For the remaining 4 quality indicators for CAP, a moderately positive effect of the intervention was detected (table 3). Timeliness of antibiotic administration increased significantly (from 55.2% to 62.9%; *P* = .03). For AECB, “not prescribing macrolides” was already optimal at baseline. Optimal duration of administering antibiotics for AECB increased 11.2% (from 25.8% to 37%) in our IHs (table 4).

## DISCUSSION

Considering the barriers to guidelines on judicious use of antibiotics during the conception, dissemination and implementation of a multifaceted intervention strategy and tailoring this strategy to the aspects that were most in need of improvement had an impact on the quality of antibiotic treatment of patients hospitalized with LRTI.

We found that, for some quality indicators, a significant and clinically relevant improvement could be achieved. For other indicators, such as streamlining therapy, there was no statistically significant improvement, but there was a trend towards better performance in the intervention group. Switch therapy also greatly improved in control hospitals. This increase was



**Table 6. Characteristics of patients with acute exacerbation of chronic bronchitis or chronic obstructive pulmonary disease before and after intervention of treatment protocols.**

Characteristic	Baseline cohort			Postintervention cohort		
	Intervention (n = 232)	Control (n = 211)	P	Intervention (n = 269)	Control (n = 237)	P
Evaluable patients	209	193	...	232	191	...
Male sex	105 (50.5)	102 (52.8)	.64 <sup>a</sup>	121 (52.2)	110 (57.6)	.26 <sup>a</sup>
Age, mean years ± SD	69.9 ± 11.2	67.8 ± 13.6	.08 <sup>b</sup>	68.9 ± 11.3	68.5 ± 10.8	.70 <sup>b</sup>
FEV <sub>1</sub> , mean % ± SD <sup>c</sup>	47.6 ± 16.0	48.1 ± 16.5	.81 <sup>b</sup>	46.7 ± 16.9	47.1 ± 18.1	.852 <sup>b</sup>
Oxygen saturation, mean % ± SD	93.7 ± 4.9	91.5 ± 5.5	<.05 <sup>b</sup>	93.2 ± 4.7	92.7 ± 5.4	.34 <sup>b</sup>
Temperature, mean °C ± SD	37.3 ± 0.7	37.2 ± 0.7	.07 <sup>b</sup>	37.4 ± 0.8	37.1 ± 0.8	<.05 <sup>b</sup>
Pulse, mean beats/min ± SD	91.9 ± 19.9	94.6 ± 21.2	.19 <sup>b</sup>	95.4 ± 18	94.9 ± 18	.78 <sup>b</sup>
Sodium level, mean mmol/L ± SD	138.5 ± 3.8	137.9 ± 3.5	.15 <sup>b</sup>	139.2 ± 3.9	138.8 ± 4.1	.44 <sup>b</sup>
Antibiotic therapy within 30 days	51 (24.4)	65 (30.8)	.45 <sup>a</sup>	82 (35.3)	55 (28.8)	.22 <sup>a</sup>
Admission to respiratory unit	189 (90.4)	184 (95.3)	.06 <sup>a</sup>	229 (98.7)	188 (98.4)	.81 <sup>a</sup>
Hospital mortality	19 (9.1)	12 (6.2)	.28 <sup>a</sup>	10 (4.3)	5 (2.6)	.35 <sup>a</sup>
ICU admission	1 (0.5)	3 (1.6)	.19 <sup>a</sup>	5 (2.2)	0 (0.0)	.04 <sup>a</sup>
Duration of stay, median days	12.1	12.3	.82 <sup>b</sup>	11.5	11.4	.89

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. FEV<sub>1</sub>, forced expiratory volume in 1 s; ICU, intensive care unit.

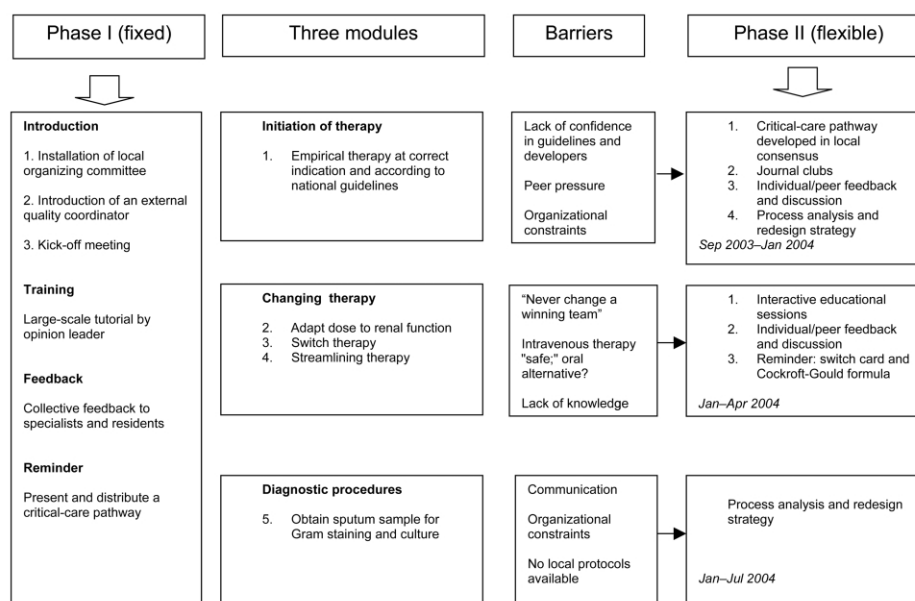
<sup>a</sup> Determined using  $\chi^2$  test.

<sup>b</sup> Determined using Student's *t* test or Mann-Whitney *U* test.

<sup>c</sup> Percentage of predicted value.

most obvious in one hospital, where process evaluation taught us that 2 young pulmonologists implemented a local switch protocol. In 2004, there was a key publication about the safety of intravenous-to-oral switch in the *Dutch Medical Journal* [24], and it is likely that a national trend in promoting switches in therapy was responsible for the effect that was observed in both

the IHs and CHs. An overall decrease of performance was noted for “obtaining a sputum sample,” despite our intervention. This may reflect a trend in the recent literature to question the need for diagnostic procedures, such as blood and sputum cultures, for every patient with LRTI [25, 26]. Secular trends (such as those mentioned here) can affect any study design, but one of



**Figure 2.** Flow diagram of intervention (Adherence to Guidelines for Antibiotic Use in Respiratory Tract Infections Trial; only key indicators for lower respiratory tract infection are depicted). AECEB, acute exacerbations of chronic bronchitis or chronic obstructive pulmonary disease; CAP, community-acquired pneumonia.

**Table 7. Baseline characteristics of hospitals and professionals.**

Characteristic	Intervention hospitals	Control hospitals	<i>P</i>
<b>Hospital<sup>a</sup></b>			
Mean no. of beds ± SD	522 ± 54	566 ± 80	NA
No. of teaching hospitals	2	2 <sup>b</sup>	NA
No. of antibiotic committees	1	2	NA
No. of hospitals that use local antibiotic guidelines	3	3	NA
No. of hospitals that use of national guidelines to compose local policies	1	1	NA
No. of hospitals that use routine feedback on pathogen-directed therapy	1	1	NA
No. of hospitals that had a quality improvement project during the prior 5 years	2	3	NA
No. of hospitals that had a pharmacist present at ward rounds to discuss antibiotic prescription	1	2	NA
<b>Professionals<sup>c</sup></b>			
Age, mean years ± SD	48.1 ± 6.6	49.1 ± 9.2	.69 <sup>d</sup>
Proportion of men (%)	19/24 (79.2)	23/29 (79.3)	.99 <sup>e</sup>
Mean no. of years in practice ± SD	20.4 ± 7.0	21.7 ± 9.9	.62 <sup>d</sup>
Proportion of pulmonologists (%)	13/25 (52)	15/29 (51.7)	.98 <sup>e</sup>
Clinical experience, proportion treating >25 patients with CAP per year (%)	16/23 (69.6)	22/28 (78.6)	.78 <sup>e</sup>
Member of local antibiotic committee, ratio (%)	1/23 (4.3)	4/28 (14.3)	.24 <sup>e</sup>
Special task in guideline composition, proportion (%)	6/23 (26.1)	10/27 (37.0)	.41 <sup>e</sup>

**NOTE.** CAP, community-acquired pneumonia; NA, not applicable.

<sup>a</sup> Data are for 3 hospitals in both the intervention and the control groups.

<sup>b</sup> Value during postintervention; hospital 5 became a teaching hospital during the intervention period.

<sup>c</sup> Twenty-five professionals in the hospital group and 29 in the control group.

<sup>d</sup> Determined using Student's *t* test.

<sup>e</sup> Determined using  $\chi^2$  test.

the key advantages of our clustered, controlled design is that it prevents contamination between the intervention and control groups; therefore, changes in the control group can be more reliably attributed to external secular trends [27].

Our results confirm those of other studies that have evaluated the effectiveness of quality improvement strategies for the treatment of LRTI [28–30]. Our results agree with a study by Halm et al. [28] that showed the partial and limited impact of a quite comparable, multifactorial intervention strategy. However, the study had no control group. In a randomized, controlled study, Yealy et al. [31] investigated the effects of increasing the intensity of guideline-implementation strategies on recommended processes of treatment; the implementation strategy with the highest intensity most closely resembles our strategy. The highest intensity strategy showed a benefit for all of the recommended processes of treatment that was much larger (60.9%) than that of our strategy, in which overall performance in the intervention group increased from 22.1% to 29.1%. Unfortunately, in the study by Yealy et al. [31], no preintervention data were collected, and therefore, possibly large institutional differences at baseline were not taken into account.

In previous studies, quality indicators were based on data elements that were easy to collect. This may have increased the feasibility of the inclusion of large numbers of patients; however, it may have also compromised the exactness of “what really happened at the bedside of the patient.” For example,

the median number of days of intravenous therapy is often used as an easy-to-measure outcome for a timely switch from intravenous to oral therapy. However, measuring professional practice “close to the patient” by studying sequential antibiotic prescriptions in detail for every patient (thus including correct decisions not to switch from intravenous to oral therapy—e.g., for patients with septicemia or lung empyema) more exactly described the quality of actual treatment provided. This allowed us to further clarify which aspect of the process underlying the indicator failed and, thus, helped us to better target our intervention strategy.

Nonetheless, our study has some limitations. First, the absence of systematic data sources at Dutch hospitals and the use of elaborate, time-consuming data collection methods limited our number of study hospitals. Thus, it was difficult to enroll the required number of patients to participate in some important processes of treatment for both CAP and AECB. Second, our study was only designed to assess changes in performance on the basis of process-of-care indicators. Although we included patient-outcome parameters in our data collection, we cannot draw any conclusions from the results of these parameters, other than that our intervention was probably safe. However, some process indicators have proven to be firmly associated with improved survival and may thus be regarded as surrogates for patient outcome [32]. Third, although our intervention showed improvement in processes of treatment, it remains unclear which

specific parts of our complex, multifaceted intervention contributed to the limited success. Again, with the limited number of hospitals, a  $\geq 3$ -arm design was not feasible. We assumed, however, that such combined interventions are needed to achieve changes in complex problems, such as the inappropriate use of antibiotics. Meticulous process evaluation in all of the IHs enabled us to detect some successful aspects of the intervention. Finally, our study design does not provide any information about the sustainability of the performance improvements. No remeasurement was performed during the year following the intervention. Future studies should focus on this important aspect of implementation research.

Although our intervention was shown to be successful in a randomized, controlled setting, the enormous efforts to collect adequate data illustrates the limited feasibility of this type of study and makes this study quite unique. Performance of high-quality, cluster-randomized, controlled trials with different arms of intervention and the prospective collection of data (that are measured close to the patient) regarding aspects of treatment require large patient cohorts and, thus, appropriate funding [33, 34]. Other designs, like time-series intervention analysis, may prove to be more cost-effective for achieving a comparable level of evidence [27, 35].

In conclusion, the implication of our work is that tailoring interventions can improve the quality of antibiotic use for patients hospitalized with LRTI. We therefore recommend that—however time-consuming this may seem—possible areas in need of improvement and barriers to change be extensively explored before clinical guidelines or changes in patient treatment are implemented.

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## APPENDIX

### FROM BARRIERS TO AN INTERVENTION STRATEGY

For the recommendation “starting empirical therapy at a correct indication and according to national guidelines,” the following different barriers that need to be overcome were reported: (1) doctors’ disagreements with current national guideline recommendations (these were because of a reported

lack of evidence justifying the recommendations and a lack of confidence in the guideline developers), and (2) peer pressure among doctors about empirical antibiotic choice (notably, at end-of-shift meetings).

To overcome these barriers, representatives of all the relevant clinical specialties should participate in developing a local consensus guideline on the basis of the available evidence, which should lead to clear and unequivocal critical-care pathways for both CAP and AECB. Journal clubs should be organized to discuss controversies in the literature about the preferred antibiotic management of CAP and the indications of antibiotic use for AECB. A 1-h feedback and tutorial session should be organized for the colleagues, in which peers compare their personal performances with respect to guideline adherence and discuss differences.

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