THE LANCET
Infectious Diseases

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Schweitzer VA, van Heijl I, Boersma WG, et al. Narrow-spectrum antibiotics for community-acquired pneumonia in Dutch adults (CAP-PACT): a cross-sectional, stepped-wedge, cluster-randomised, non-inferiority, antimicrobial stewardship intervention trial. *Lancet Infect Dis* 2021; published online Oct 7. http://dx.doi.org/10.1016/S1473-3099(21)00255-3.

Supplementary appendix to the manuscript

Narrow-spectrum antibiotics for community-acquired pneumonia in adults: a cross-sectional stepped-wedge cluster randomised antimicrobial stewardship intervention trial

Table of contents:

Table S1: Pathogens detected in patients admitted with CAP

	Control (N = 2235)		**Intervention (N = 1849)**	
	Proven	**Possible**	**Proven**	**Possible**
Streptococcus pneumoniae	205 (9.1%)	46 (2.0%)	188 (10.2%)	49 (2.7%)
Staphylococcus aureus	9 (0.4%)	32 (1.4%)	11 (0.6%)	45 (2.4%)
Other gram-positives	19 (0.9%)	18 (0.8%)	24 (1.3%)	5 (0.3%)
Haemophilus influenzae	4 (0.2%)	137 (6.1%)	7 (0.4%)	137 (7.4%)
Moraxella catarrhalis	-	20 (0.9%)	-	29 (1.6%)
Escherichia coli	17 (0.8%)	29 (1.3%)	13 (0.7%)	22 (1.2%)
Klebsiella pneumoniae	3 (0.1%)	11 (0.5%)	1 (0.1%)	18 (1.0%)
Pseudomonas aeruginosa	2 (0.1%)	35 (1.6%)	-	29 (1.6%)
Other gram-negatives	8 (0.4%)	65 (2.9%)	13 (0.7%)	78 (4.2%)
Legionella pneumophila	28 (1.2%)	-	22 (1.2%)	-
Mycoplasma pneumoniae	-	-	-	2 (0.1%)
Mycobacteria	-	2 (0.1%)	-	2 (0.1%)
Aspergillus species	-	16 (0.7%)	-	22 (1.2%)
Other fungi / yeast	-	2 (0.1%)	1 (0.1%)	3 (0.2%)
No pathogen		1641 (73.4%)		1279 (69.2%)

Proven pathogens: based on pathogens detected in blood cultures, pleural fluid cultures, and urinary antigen tests (for *S. pneumoniae* and *L. pneumophila*).

Possible pathogens: based on pathogens detected in sputum cultures,

bronchoalveolar lavage fluid cultures, PCR, and serology. No data on viral pathogens available.

Table S2: Stewardship implementation

	Intervention (n=1,849)
Education	
E-learnings completed	235 (45.2%)
Clinical lessons performed	54
Audit and feedback	
Patients eligible for feedback	591 (32.0 %)
Recommendations given	330 (55.8%)
Accepted	197 (59.7%)
Rejected	133 (40.3%)
Reasons for not following advice:	
Antibiotics discontinued	5 (3.8 %)
Patient discharged or deceased	4 (3.0%)
Penicillin allergy	2 (1.5 %)
Legionella risk factors	2 (1.5 %)
Advice of microbiologist	1 (0.8%)
Severe pneumonia by PSI/CURB score / clinical deterioration	9 (6.8%)
COPD*	11 (8.3%)
Suspected resistant pathogen	9 (6.8%)
Treatment based on resistant pathogen in new culture	6 (4.5%)
Treatment based on resistant pathogen in previous culture	2 (1.5 %)
Pneumococcal urine antigen test is negative	8 (6.0%)
Pneumococcal urine antigen test forgotten	5 (3.8%)

Supervisor wants to continue antibiotics	7 (5.3%)
Reason not clear	52 (39.0%)
Other reasons[1]	10 (7.5%)
Recommendations given by	
Telephone	244 (74.0%)
Medical record	17 (5.1%)
Both	69 (20.9%)
No recommendations given	261 (44.2%)
Reasons for no advice given	
Severe pneumonia by PSI/CURB score / clinical deterioration	56 (21.5%)
COPD[*]	12 (4.6%)
Suspected resistant pathogen	21 (8.0%)
Treatment based on resistant pathogen in old culture	39 (14.9%)
No time to give advice / missed	42 (16.1%)
Reason not clear	28 (10.7%)
Other reasons[2]	63 (24.1%)
Patients not eligible for feedback	1258 (68.0%)
Reasons for not eligible	
Started with narrow-spectrum antibiotics	866 (68.8%)
Switched to narrow-spectrum antibiotics	89 (7.1%)
Antibiotics discontinued	11 (0.9%)
Patient discharged or deceased	31 (2.5%)
Penicillin allergy	125 (9.9%)
Legionella risk factors	107 (8.5%)
Advice of microbiologist	29 (2.3%)

Second recommendations given	13 (3.9%)
Accepted	3 (0.9%)
Rejected	10 (3.0%)
Recommendations given by	
Telephone	6 (46.2%)
Medical record	5 (38.5%)
Both	2 (15.4%)

* Chronic Obstructive Pulmonary Disease

1: Other reasons for rejecting advice; due to hospital-acquired pneumonia (not according to official risk factors), due to possible other focus, due to recurrent pneumonia, post-obstructive pneumonia, bronchiectasis or awaiting culture results.

2: Other reasons for no advice given: hospital-acquired pneumonia (not according to guideline risk factors), patient immunocompromised (not according to our definitions), suspected empyema, patient is agitated, possible other focus, awaiting culture results, post-obstructive pneumonia, due to legionella risk factors (not according to guideline risk factors), all cultures negative, possible abscess, continuing treatment of general practitioner.

Table S3: Adjusted relative reductions in broad-spectrum DOT per hospital

	Broad-spectrum DOT (median, IQR)			Empirical narrow-spectrum (proportion)	
	Control	Intervention		Control	Intervention
Hospital*	Median (IQR)	Median (IQR)	Adjusted relative reductions	%	%
L	4 (1-9)	4 (1-9)	0.225	29.2%	28.1%
K	4 (0-8)	3 (0-8)	0.170	47.9%	52.0%
J	2 (0-7)	0 (0-5)	0.167	59.2%	69.1%
H	8 (3-9)	5 (2-9)	0.286	14.7%	27.3%
F	8 (3-11)	3 (0-8)	0.393	16.2%	43.6%
D	4 (0-8)	3 (0-8)	0.219	39.1%	49.5%
C	8 (4-11)	2 (0-8)	0.376	20.5%	48.3%
B	6 (0-9)	3 (0-8)	0.259	31.8%	60.0%
A	7 (2-9)	2 (0-8)	0.284	26.7%	63.6%
Total	6 (2-9)	3 (0-8)	0.269	28.8%	45.9%

* Hospitals E, G and I stopped before the intervention period. The hospital names are equal to the names used in the randomisation scheme in Figure S1.

Table S4: Specification of antibiotics given as empirical treatment

	Control (n=2,235)	Intervention (n=1,849)
Narrow-spectrum		
Penicillin	19 (0.9%)	29 (1.6%)
Amoxicillin	548 (24.5%)	745 (40.3%)
Doxycycline	73 (3.3%)	66 (3.6%)
Broad-spectrum		
Beta-lactams		
Amoxicillin – clavulanic acid	426 (19.0%)	244 (13.2%)
Ceftriaxone	114 (5.1%)	111 (6.0%)
Cefuroxime	149 (6.7%)	91 (4.9%)
Cefotaxime	-	-
Ceftazidime	12 (0.5%)	6 (0.3%)
Cefazolin	1 (0.0%)	-
Piperacillin/tazobactam	10 (0.4%)	2 (0.1%)
Macrolides		
Azithromycin	9 (0.4%)	3 (0.2%)
Clarithromycin	10 (0.4%)	-
Erythromycin	-	1 (0.1%)
Fluoroquinolones		
Moxifloxacin	62 (2.8%)	22 (1.2%)
Levofloxacin	4 (0.2%)	-
Ciprofloxacin	20 (0.9%)	13 (0.7%)

Other		
Co-trimoxazole	10 (0.4%)	12 (0.6%)
Clindamycin	2 (0.1%)	-
Combination therapy		
Amoxicillin + ciprofloxacin	153 (6.8%)	122 (6.6%)
Penicillin + ciprofloxacin	211 (9.4%)	159 (8.6%)
Amoxicillin– clavulanic acid + ciprofloxacin	99 (4.4%)	60 (3.2%)
Ceftriaxone + ciprofloxacin	40 (1.8%)	20 (1.1%)
Cefuroxime + ciprofloxacin	33 (1.5%)	11 (0.6%)
Cefuroxime + erythromycin	25 (1.1%)	5 (0.3%)
Cefuroxime + clarithromycin	23 (1.0%)	1 (0.1%)
Amoxicillin + cefuroxime	14 (0.6%)	14 (0.8%)
Amoxicillin + penicillin + ciprofloxacin	12 (0.5%)	9 (0.5%)
Amoxicillin– clavulanic acid + penicillin + ciprofloxacin	13 (0.6%)	12 (0.6%)
Other*		103 (5.6%)

* All other combination therapies below N = 10.

Table S5: Crude, adjusted for design, and fully adjusted risk differences in all-cause 90-day mortality

90-day mortality	Control (n=2,235)	Intervention (n=1,849)	Crude RD	Adjusted for design RD*	Fully adjusted** RD
N (%)	242 (10.9%)	199 (10.8%)			
Intention-to-treat					
90%CI			-0.09% (-1.7% to 1.5%)	0.9% (-2.3% to 3.2%)	0.4% (-2.7% to 2.4%)
95%CI			-0.09% (-2.0% to 1.8%)	0.9% (-2.9% to 3.7%)	0.4% (-3.3% to 2.8%)
As-treated					
90%CI			-3.1% (-4.6% to -1.4%)	-3.1% (-4.8% to -1.4%)	0.07% (-1.8% to 1.7%)
95%CI			-3.1% (-4.9% to -1.1%)	-3.1% (-5.1% to -1.1%)	0.07% (-2.1% to 2.1%)
CACE***					
90%CI			-0.5% (-12.6% to 10.1%)	5.4% (-13.9% to 19.1%)	2.2% (-15.8% to 13.7%)
95%CI			-0.5% (-15.0% to 12.1%)	5.4% (-17.0% to 22.7%)	2.2% (-19.2% to 16.4%)

* Adjusted for design and time, ** also adjusted for possible confounders, *** Complier Average Causal Effect.

RD: risk differences

Table S6: Sensitivity analyses for patients with radiologically confirmed CAP.

Radiologically confirmed CAP	Fully adjusted* analysis
90-day mortality	RD: 1.8% (90% CI: -1.3% to 4.3%)
Broad-spectrum DOT	AR: -1.9 (95% CI: -2.6 to -1.1) RR: 26.8% (95% CI: 17.8% to 36.7%)
Doxycyclin classified as broad-spectrum antibiotic	
90-day mortality	RD: -0.2% (90% CI: -2.1% - 1.5%)
Broad-spectrum DOT	AR: -1.7 (95% CI: -2.4 to -1.1) RR: 26.6% (95% CI: 18.1% to 35.3%)

* Adjusted for design, time and for possible confounders.

RD: risk differences, RR: relative reductions, AR: absolute reductions

Table S7: Crude, adjusted for design and fully adjusted risk differences in 30-day mortality

30-day mortality	Control (n=2,235)	Intervention (n=1,849)	Crude RD	Adjusted for design RD*	Fully adjusted** RD
N (%)	154 (6.9%)	123 (6.7%)			
Intention-to-treat					
90%CI			-0.3% (-1.6% to 1.1%)	-0.7% (-2.9% to 1.2%)	-1.1% (-3.1% to 0.7%)
95%CI			-0.3% (-1.8% to 1.3%)	-0.7% (-3.3% to 1.6%)	-1.1% (-3.5% to 1.1%)
As-treated					
90%CI			-2.6% (-4.0% to -1.4%)	-2.6% (-4.0% to -1.4%)	-0.3% (-1.8% to 1.1%)
95%CI			-2.6% (-4.2% to -1.1%)	-2.6% (-4.2% to -1.1%)	-0.3% (-2.0% to 1.4%)
CACE***					
90%CI			-1.5% (-9.1% to 6.1%)	-3.9% (-17.0% to 7.6%)	-6.4% (-18.5% to 4.2 %)
95%CI			-1.5% (-10.6% to 7.5%)	-3.9% (-19.4% to 10.0%)	-6.4% (-20.8% to 6.2%)

* Adjusted for design and time, ** also adjusted for possible confounders, *** Complier Average Causal Effect.

RD: risk differences

Table S8. Complications of patients with CAP hospitalised to a non-ICU ward in the control compared to the intervention period

	Control (n=2,235)	Intervention (n=1,849)
Pleural effusion	398 (17.8%)	326 (17.6%)
Organ failure	78 (3.5%)	87 (4.7%)
Clostridioides difficile associated disease	56 (2.5%)	45 (2.4%)
Empyema	22 (1.0%)	23 (1.2%)
Septic shock	12 (0.5%)	4 (0.2%)
Acute respiratory distress syndrome	10 (0.5%)	7 (0.4%)
Pneumothorax	9 (0.4%)	3 (0.2%)
Lung abscess	9 (0.4%)	1 (0.1%)
Other	244 (10.9%)	205 (11.1%)

Table S9: Post-hoc specification of antibiotics given as empirical treatment for patients with COPD/asthma

	Control (n=968)	Intervention (n=878)
Narrow-spectrum		
Penicillin	6 (0.6%)	13 (1.5%)
Amoxicillin	194 (20.0%)	343 (39.0%)
Doxycycline	36 (3.7%)	38 (4.3%)
Broad-spectrum		
Beta-lactams		
Amoxicillin – clavulanic acid	247 (25.5%)	147 (16.7%)
Ceftriaxone	52 (5.4%)	62 (7.1%)
Cefuroxime	54 (5.6%)	41 (4.7%)
Ceftazidime	10 (1.0%)	6 (0.7%)
Cefazolin	1 (0.1%)	-
Piperacillin/tazobactam	6 (0.6%)	1 (0.1%)
Macrolides		
Azithromycin	4 (0.4%)	1 (0.1%)
Clarithromycin	6 (0.6%)	-
Fluoroquinolones		
Moxifloxacin	22 (2.3%)	9 (1.0%)
Levofloxacin	4 (0.4%)	-
Ciprofloxacin	11 (1.1%)	6 (0.7%)
Other		

Co-trimoxazole	5 (0.5%)	9 (1.0%)
Clindamycin	1 (0.1%)	-
Combination therapy		
Amoxicillin + ciprofloxacin	48 (5.0%)	52 (5.9%)
Penicillin + ciprofloxacin	87 (9.0%)	63 (7.2%)
Amoxicillin– clavulanic acid + ciprofloxacin	41 (4.2%)	19 (2.2%)
Ceftriaxone + ciprofloxacin	10 (1.0%)	4 (0.5%)
Cefuroxime + ciprofloxacin	13 (1.3%)	5 (0.6%)
Cefuroxime + erythromycin	10 (1.0%)	2 (0.2%)
Cefuroxime + clarithromycin	12 (1.2%)	-
Amoxicillin + cefuroxime	5 (0.5%)	2 (0.2%)
Amoxicillin + penicillin + ciprofloxacin	3 (0.3%)	4 (0.5%)
Other*	80 (8.3%)	51 (5.8%)

Table S10: Post-hoc specification of antibiotics given as empirical treatment for patients treated with antibiotics in the two weeks before hospital admission

	Control (n=686)	Intervention (n=549)
Narrow-spectrum		
Penicillin	4 (0.6%)	7 (1.0%)
Amoxicillin	102 (21.4%)	153 (14.9%)
Doxycycline	32 (4.7%)	30 (4.4%)
Broad-spectrum		
Beta-lactams		
Amoxicillin – clavulanic acid	144 (21.0%)	87 (12.7%)
Ceftriaxone	39 (5.7%)	41 (6.0%)
Cefuroxime	39 (5.7%)	35 (5.1%)
Ceftazidime	8 (1.2%)	4 (0.6%)
Piperacillin/tazobactam	5 (0.7%)	1 (0.1%)
Macrolides		
Azithromycin	6 (0.9%)	2 (0.3%)
Clarithromycin	4 (0.6%)	-
Fluoroquinolones		
Moxifloxacin	43 (6.3%)	12 (1.7%)
Levofloxacin	2 (0.3%)	-
Ciprofloxacin	10 (1.5%)	7 (1.0%)
Other		
Co-trimoxazole	3 (0.4%)	6 (0.9%)

Clindamycin	2 (0.3%)	-
Combination therapy		
Amoxicillin + ciprofloxacin	45 (6.6%)	37 (5.4%)
Penicillin + ciprofloxacin	55 (8.0%)	50 (7.3%)
Amoxicillin– clavulanic acid + ciprofloxacin	46 (6.7%)	32 (4.7%)
Ceftriaxone + ciprofloxacin	13 (1.9%)	14 (2.0%)
Cefuroxime + ciprofloxacin	13 (1.9%)	4 (0.6%)
Cefuroxime + erythromycin	5 (0.7%)	1 (0.1%)
Cefuroxime + clarithromycin	10 (1.5%)	-
Other*	56 (8.2%)	26 (4.7%)

Table S11: Post-hoc specification of antibiotics given as empirical treatment for patients admitted during the influenza season (week 1 till 11 in 2015/2016, week 48 till 10 in 2016/2017)

	Control (n=1062)	Intervention (n=549)
Narrow-spectrum		
Penicillin	8 (0.8%)	2 (0.3%)
Amoxicillin	269 (25.3%)	244 (38.4%)
Doxycycline	37 (3.5%)	19 (3.0%)
Broad-spectrum		
Beta-lactams		
Amoxicillin – clavulanic acid	156 (14.7%)	75 (11.8%)
Ceftriaxone	48 (4.5%)	41 (6.4%)
Cefuroxime	56 (5.3%)	33 (5.2%)
Ceftazidime	5 (0.5%)	2 (0.3%)
Piperacillin/tazobactam	1 (0.1%)	-
Macrolides		
Azithromycin	5 (0.5%)	1 (0.2%)
Clarithromycin	5 (0.5%)	-
Fluoroquinolones		
Moxifloxacin	43 (4.0%)	13 (2.0%)
Levofloxacin	2 (0.2%)	-
Ciprofloxacin	4 (0.4%)	5 (0.8%)
Other		
Co-trimoxazole	8 (0.8%)	9 (1.4%)

Clindamycin	2 (0.2%)	-
Combination therapy		
Amoxicillin + ciprofloxacin	59 (5.6%)	36 (5.7%)
Penicillin + ciprofloxacin	108 (10.2%)	46 (7.2%)
Amoxicillin– clavulanic acid + ciprofloxacin	44 (4.1%)	16 (2.5%)
Ceftriaxone + ciprofloxacin	13 (1.2%)	4 (0.6%)
Cefuroxime + ciprofloxacin	19 (1.8%)	6 (0.9%)
Cefuroxime + erythromycin	11 (1.0%)	-
Cefuroxime + clarithromycin	11 (1.0%)	-
Other*	148 (13.9%)	84 (13.2%)

Table S12: Crude, adjusted for design and fully adjusted relative risk reductions in broad-spectrum DOT using mixed effect negative binomial regression as pre-defined in the statistical analysis plan

	Control (n=2,240) Median (IQR)	Intervention (n=1,844) Median (IQR)	Crude RRR (95% CI)	Adjusted for design RRR* (95% CI)	Fully adjusted** RRR (95% CI)
Broad-spectrum DOT	6 (2-9)	3 (0-8)	20.2% (9.2% to 29.8%)	28.1% (15.5% to 38.9%)	26.9% (15.4% to 37.4%)

* Adjusted for design and time, ** also adjusted for possible confounders.

Table S13. Adherence to the antimicrobial stewardship bundle components e-learning and clinical lessons per hospital. Adherence to the e-learning is displayed as the number of e-learning completed compared to the number of doctors invited. Adherence to the clinical lessons is displayed as the average attendance per clinical lesson.

Hospital	E-learning completed/ invited (n, %)	Clinical lessons Average attendance per clinical lesson (%)
L	5/37 (13.5%)	28.4%
K	18/57 (31.6%)	10.5%
J	30/57 (52.6%)	30.7%
H	49/68 (72.1%)	32.3%
F	40/63 (63.5%)	38.1%
D	14/55 (25.5%)	52.7%
B	1/48 (2.1%)	11.0%
C	42/120 (35.0%)	27.5%
A	6/15 (40.0%)	46.7%

Figure S1: Stepped-wedge randomisation scheme

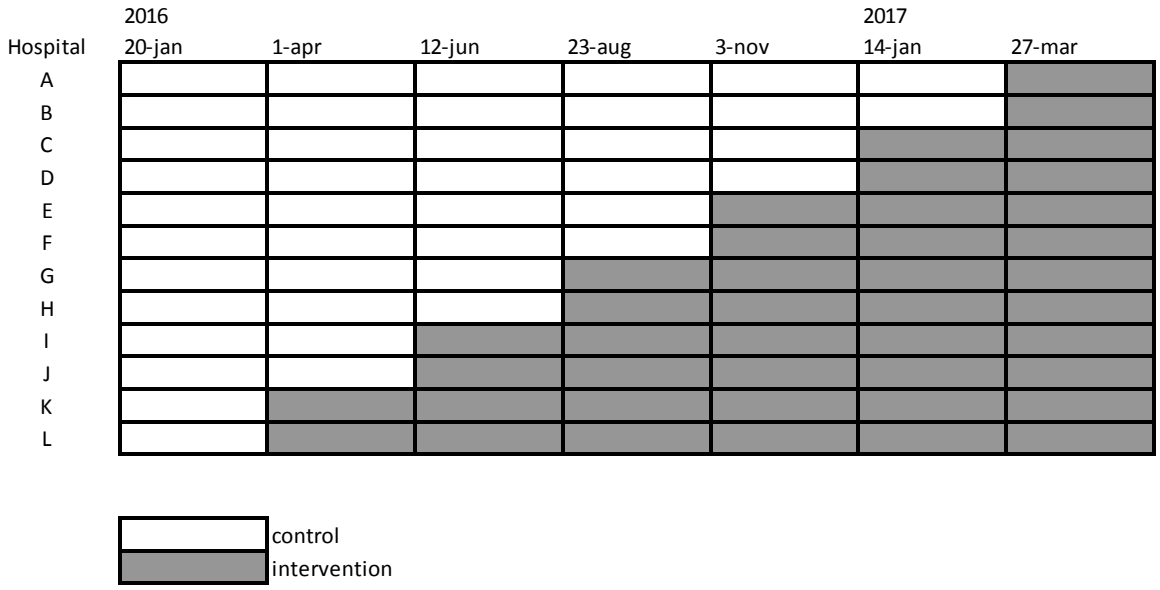
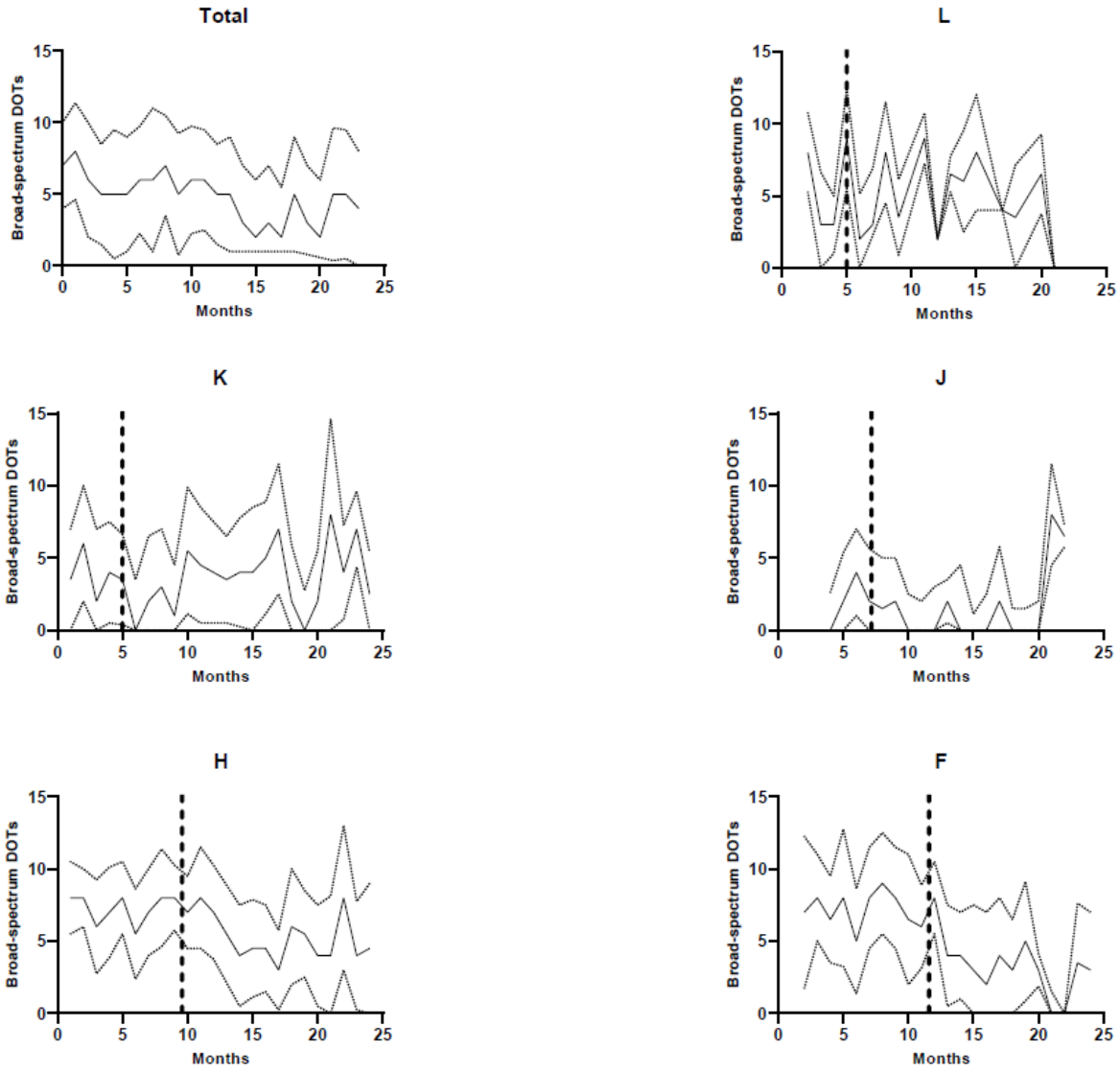
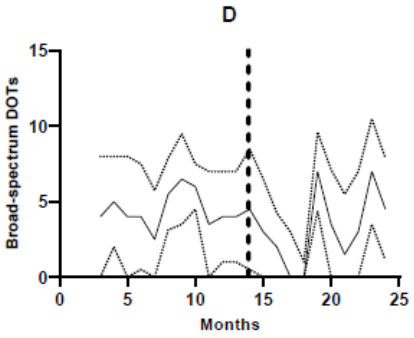


Figure S2: Time series of the total and per hospital median broad-spectrum DOT per patient. Solid lines indicate the median broad-spectrum DOTs per patient in time intervals of months. Horizontal dashed lines indicate the corresponding interquartile ranges. Vertical dashed lines indicate the start of the intervention period in the corresponding hospitals.

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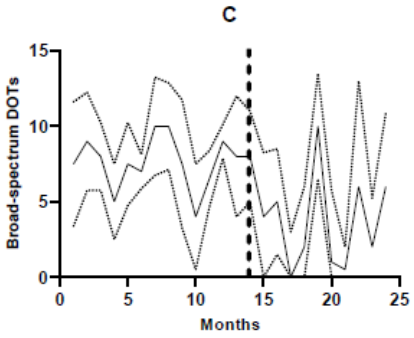
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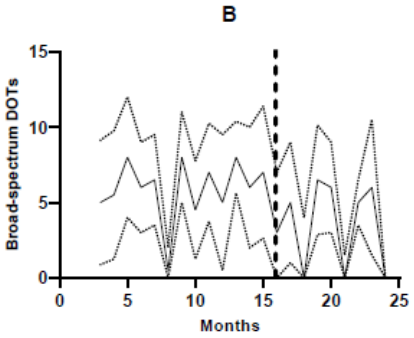
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Months
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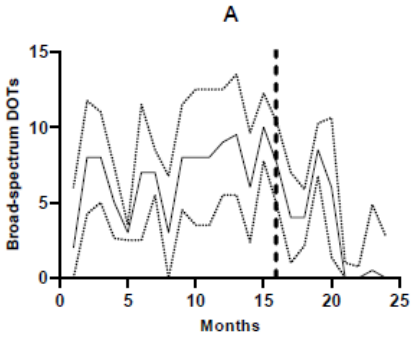
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Broad-spectrum DOTs
Months
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This supplement contains the following items:

1. Original protocol (version 3, 22-07-2015), final protocol (version 4, 01-03-2016), summary of changes.

2. Original and final statistical analysis plan

CAP-PACT study:

Community-acquired pneumonia: increasing protocol adherence by antibiotic stewardship in a stepped wedge cluster-randomized trial

Community-acquired Pneumonia
PACT
Antibiotic Stewardship Intervention Program

Version 3, July 2015

PROTOCOL TITLE: Community-acquired pneumonia: increasing protocol adherence by antibiotic stewardship in a stepped wedge cluster-randomized trial

Protocol ID: 1
Short title: CAP-PACT
Version: 2
Date: 22-07-2015

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Coordinating investigators of participating centers:

<To be determined>

Sponsor:	Investigator initiated
Subsiding party:	<>
Independent expert:	<>

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Head of Department:		
Principal Investigator:		

TABLE OF CONTENTS

SUMMARY

Rationale:

Community-acquired pneumonia (CAP) is a common acute lower respiratory tract infection associated with high mortality and morbidity. The optimal empirical therapy for moderately-severe CAP is amoxicillin or penicillin, as is advocated in the Dutch national guideline. However, adherence to the CAP guideline is low in clinical practice and many patients get treated with unnecessary broad-spectrum antibiotics. Unnecessary use of broad-spectrum antibiotics leads to an increase of antibiotic resistance, healthcare costs and complications. As a consequence, reducing excessive use of broad-spectrum antibiotics has been a major focus for antibiotic stewardship programs worldwide. Antibiotic stewardship promotes appropriate antibiotic use by implementing quality improvement programs and has proven to be effective and cost-effective in doing so.

Objective:

In this study, we aim to increase guideline adherence in moderately severe CAP patients by a multifaceted antibiotic stewardship intervention. By increasing guideline adherence we aim to show a reduction in broad-spectrum antibiotic use and non-inferiority in clinical outcome.

Study design:

Stepped wedge cluster randomized trial

Study population:

Patients hospitalized for CAP on a non-intensive care ward

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A multifaceted intervention bundle consisting of education, adaptation of a pragmatic disease severity classification and prospective real-time audit and feedback will be introduced.

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- Days on broad-spectrum antibiotics
- 30-day mortality

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There is no increased burden or risk associated with this study as patients will be treated as standard of care.

1. INTRODUCTION AND RATIONALE

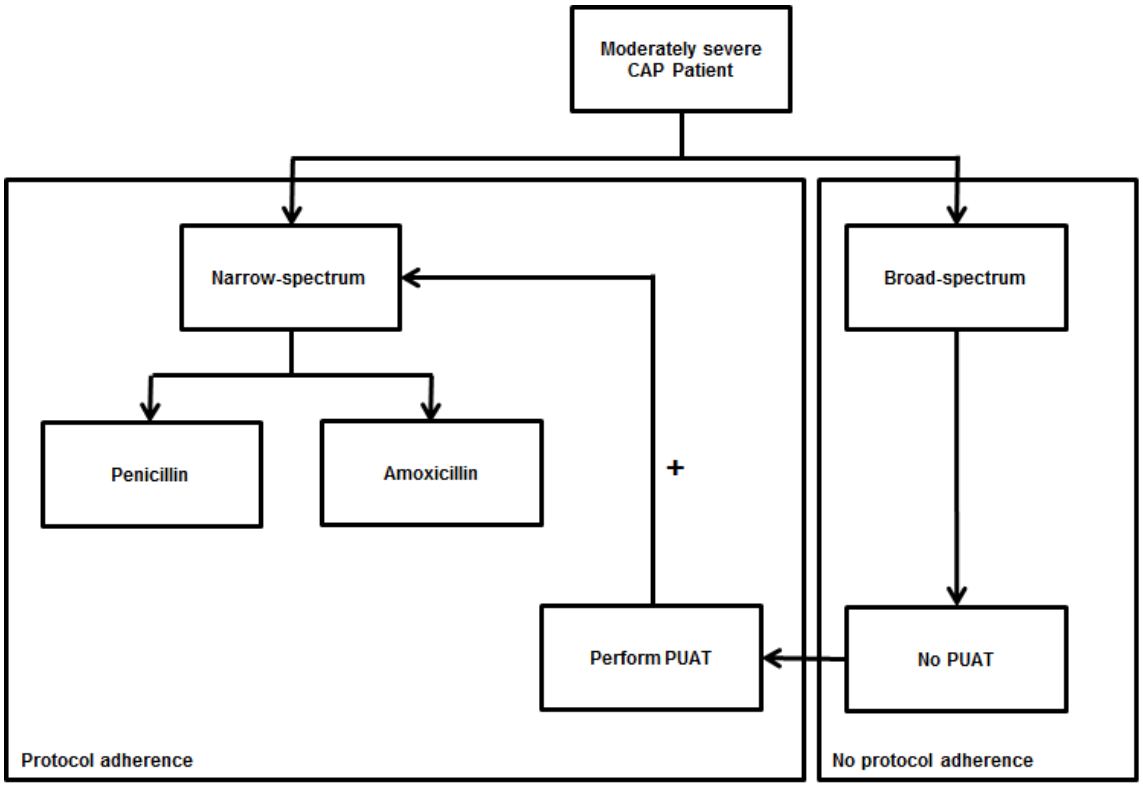
Community-acquired pneumonia (CAP) is an acute lower respiratory tract infection associated with high mortality and morbidity (1, 2). The incidence of CAP is high, making it the leading cause of infection associated mortality in developed countries (1-3). The disease severity of CAP is assessed by three classifications in the national guidelines without prioritizing any: the pragmatic classification, the PSI score or the CURB-65 score (2). The pragmatic disease severity classifies patients as mild (no hospital admission), moderately severe (hospital admission) or severe (ICU admission). The disease severity determines the empirical treatment of patients as is advised in the national guideline (Table 1).

Table 1. Advised antibiotic treatment regimens for different CAP severities by national SWAB guidelines

	Mild CAP	Moderately severe CAP	Severe CAP
First choice	amoxicillin p.o.	amoxicillin i.v.	moxifloxacin i.v or levofloxacin i.v.
Second choice	doxycyclin p.o.	penicillin i.v.	penicillin i.v./ amoxicillin i.v. and ciprofloxacin i.v.
Third choice			3rd generation cephalosporin i.v. and macrolide i.v.

Adherence to the CAP guideline is low, varying between 30,5% and 62,9% depending on the disease severity classification used (18). From these disease severity classifications, the pragmatic classification is the easiest in use, most sparse in broad-spectrum antibiotic use and has the highest adherence in clinical practice (18). Non adherence to the guidelines is largely explained by overtreatment with broad-spectrum antibiotics (12, 18). Adherence to the guideline might be improved by increasing diagnostic certainty with the pneumococcal urine antigen test (PUAT) (Figure 1). The PUAT is a quick (<15 minutes) and reliable way to diagnose CAP caused by *S. pneumoniae*, with a sensitivity of 74% and specificity of 97,2% (15). In case of a positive result, the PUAT justifies save streamlining to penicillin due to low *S. pneumoniae* penicillin resistance in the Netherlands (0,3%)(2). Currently, the PUAT is commonly not performed or consequential streamlining is lacking, with as little as 35% of positive PUATs resulting in a change to targeted therapy (19).

Other known barriers that prevent guideline adherence include inadequate education on microbial therapy, insufficient knowledge regarding pneumonia severity tools and unfamiliarity with the guidelines (12, 13).



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A widely accepted and proven effective method to increase guideline adherence is by the means of Antibiotic Stewardship programs (21). Antibiotic Stewardship programs are currently widely deployed as specialized Antibiotic Stewardship teams become mandatory in every hospital. Stewardships interventions that are proven to be effective include educational efforts and audit and feedback (21). To date, the effect of an Antibiotic Stewardship program on the guideline adherence of CAP patients and the result on clinical outcome is unknown.

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In addition, we want to assess the following secondary objectives:

- 90-day mortality
- Length of stay
- Readmissions
- Switches from broad-spectrum antibiotics to narrow-spectrum antibiotics and vice versa
- Switches from intravenous to oral antibiotics and vice versa
- *Clostridium difficile* infections

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3.1 Study design

The design will be a stepped wedge cluster randomized trial (Figure 2).

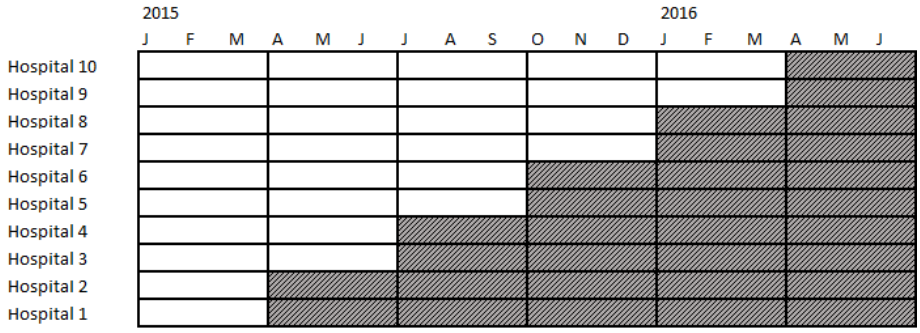

Figure 2. Stepped wedge design with a cluster size of 3 months with 10 participating hospitals.

In the stepped wedge design, hospitals will be randomly allocated to different times of intervention implementation. The stepped wedge design has several advantages. Firstly, all centers implement the Antibiotic Stewardship intervention, which is regarded as a quality improving program. It is logistically more feasible to implement the intervention bundle one at a time instead of all at once. In the stepped wedge design, the intervention effect can be estimated from both between- and within- cluster comparison, resulting in more statistical

power and a reduced required sample size (14). Lastly, but not least important for CAP, time-effects such as seasonal influences can be estimated and adjusted for by the design.

Hospitals will be randomly allocated to different times of intervention implementation. Randomization will be conducted electronically.

3.2 Inclusion procedure

Patients will be screened daily for inclusion eligibility. Initial screening will be conducted using the emergency department admission charts. Patients who get admitted to the internal medicine, geriatric or pulmonary department will be further evaluated. Inclusion of the patients will be based on the working diagnosis of the emergency department physicians.

3.3 Inclusion criteria

Patients 18 years of age or older who get a admitted to a non-ICU department are eligible for inclusion.

3.4 Exclusion criteria

- Patients aged below 18 years
- Patients who immediately get admitted to the ICU
- Residence in a nursing home or long-term care facility in the last 14 days
- Patients hospitalized in an acute care hospital for two or more days in the last 14 days
- Patients with a history of Cystic Fibrosis
- Patients where the suspected pathogen of the CAP is not treated with penicillin or amoxicillin (i.e. *Pneumocystis jiroveci.* Tuberculosis, etc.)
- Patients with immunodeficiency, defined as having one or more of the following criteria:
    - HIV infection with a last CD4 count of <300//µL
    - Cytotoxic chemotherapy or radiotherapy in the previous 3 months
    - Chronic hemodialysis > 3 months
    - History of receiving an organ or bone marrow transplant
    - Using immunosuppressive therapy, include corticosteroid treatment only when dosage is high (>0,5mg/kg/day) for a longer period of time (>14 days)

3.5 Intervention

The intervention will consist of a multifaceted antibiotic stewardship bundle formed on recommendations by the national and IDSA guidelines (17). The bundle consists of the following elements (Figure 3):

1. Education
2. Motivating opinion leaders
3. Adapting a pragmatic classification of disease severity
4. Prospective real-time audit and feedback

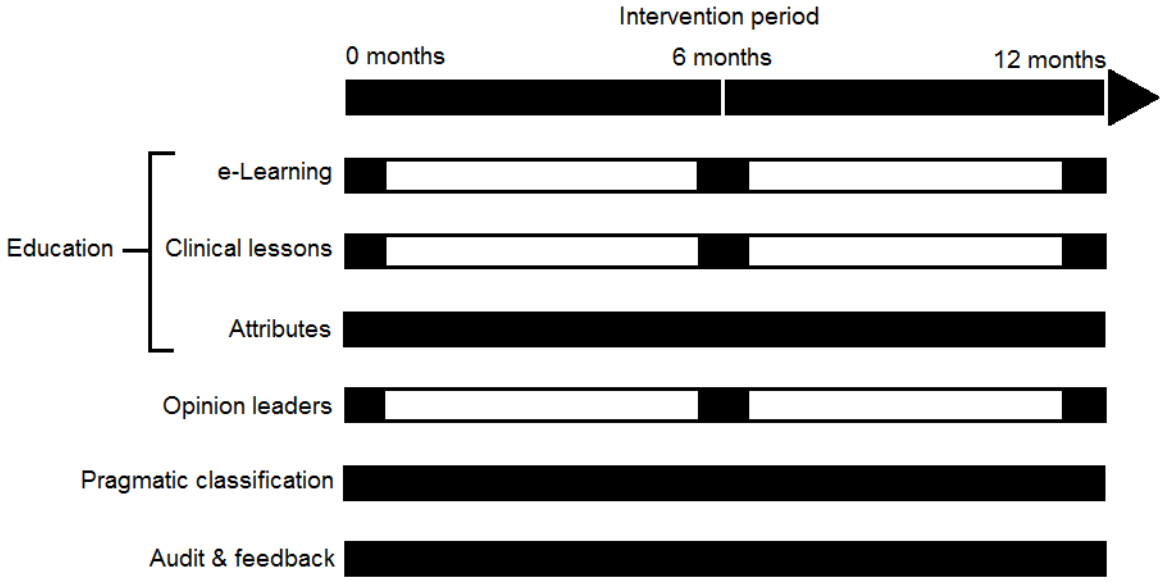

Figure 3. Timeline of intervention period with the corresponding intervals

1. Education

The education component of the intervention will be directed at physicians involved in the care of CAP patients and consist of:

1. e-Learning module
2. Clinical lessons
3. Distribution of educational attributes.

1.1 e-Learning module

We developed an e-Learning module where physicians will learn about the guideline through case-based reasoning. Response and attendance of the e-Learning will be monitored. The e-Learning will be repeated in 12 month intervals. New employees will be identified monthly and asked to participate.

1.2 Clinical lessons

Clinical lessons about the CAP guideline will be given in 6 months intervals. During these clinical lessons, physicians will be educated about the CAP guideline through case-based reasoning. In addition, previous performance as registered in the control period will be presented as feedback.

1.3 Educational attributes

Educational attributes, consisting of posters and pocket cards, will be distributed to all healthcare personnel involved in treating CAP patients at the start of the intervention. The purpose of these educational attributes will be to give clear and short overviews of how patients should be treated according to the guideline.

2. Adaptation of the pragmatic disease severity classification

The pragmatic classification is the easiest in use, most sparse in broad-spectrum antibiotic use and has the highest adherence in clinical practice (18). The intervention period will start with the promotion and implementation of the pragmatic disease severity classification. The pragmatic classification will be promoted in the other bundle components. Concomitant use of other disease severity scores is allowed to assess the general frailty of the patient. However, we strive to base the empiric treatment on the pragmatic disease severity classification.

3. Motivating opinion leaders

Opinion leaders of various departments will be identified and chosen by a local multidisciplinary panel at the start of the intervention period. These opinion leaders are the most likely to influence working behavior during routine clinical practice. Meetings will be scheduled with these opinion leaders in 6 months intervals. During these meetings, past performances and barriers that impede adherence will be discussed.

4. Audit and feedback

Prospective, real-time audit and feedback will be conducted by a local Antibiotic Stewardship team throughout the intervention period. The audit and feedback procedure will consist of daily evaluation of the antibiotic therapy of currently admitted CAP patients. The feedback to the caring physician will be done according to the following decision making flowchart (Figure 5):

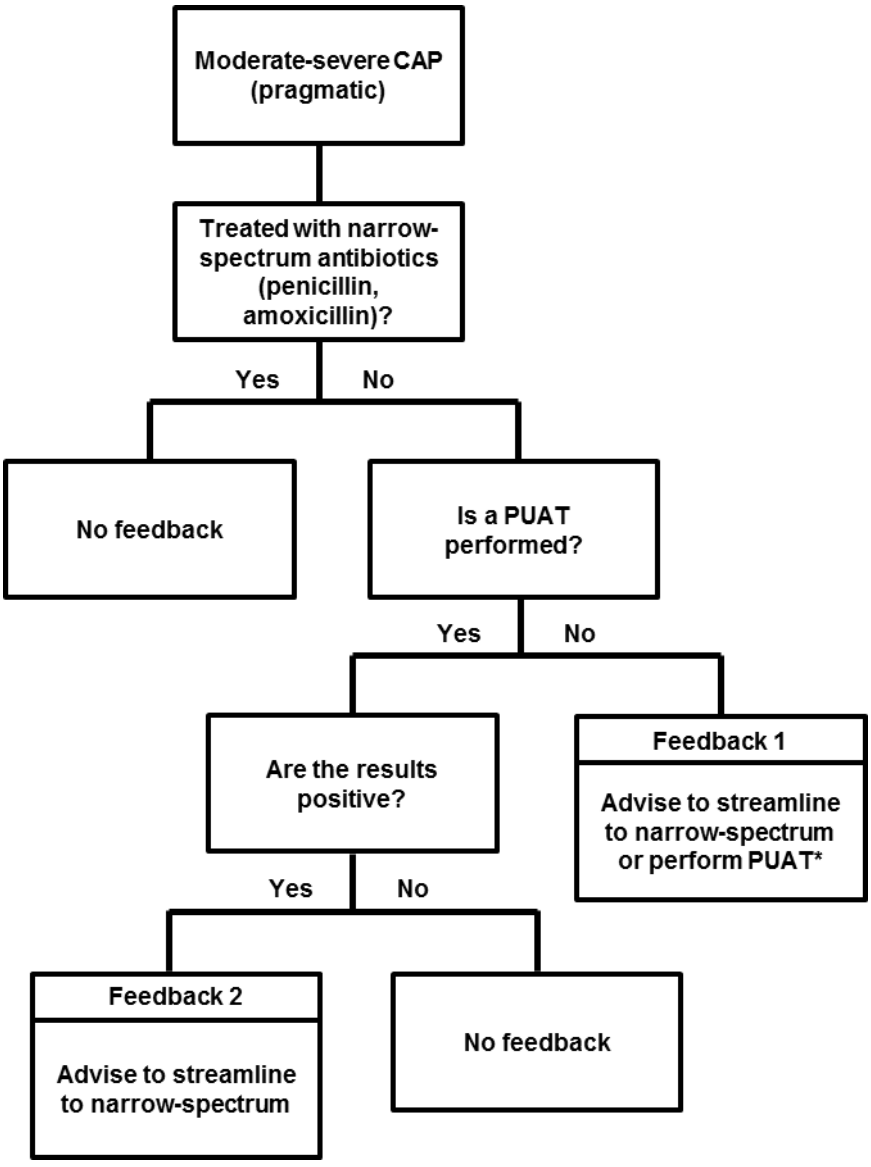

Figure 5. Decision making flowchart used in the audit and feedback procedure. Standardized feedback 1 and 2 can be found in the appendix.
**Pneumococcal urine antigen test*

The feedback will be done both personal by phone and written in the electronic patient file with standardized feedback responses (Attachment 1). If the hospital uses paper patient files, the recommendation will be printed and added to the patient file. Feedback will be given only once, with the exception of Feedback 1, where a Feedback 2 can follow after a positive pneumococcal urine antigen test (PUAT). It is important to note that the treating physician can always deviate from the given advice. Deviations with corresponding reasons will be registered in the case report form.

3.6 Data collection

Data will be entered in an electronic case report form (eCRF). On admission and inclusion the demographic data, presenting symptoms, co-morbidities, previous antibiotic use and the pneumonia severity scores will be recorded (Table 2). The Antibiotic Stewardship team advice log will be recorded when advices are given. At hospital discharge the antibiotic treatment received, culture results and feedback results will be recorded. The 30- and 90-day mortality will be registered 30 and 90 days after inclusion.

Table 2. Data collection overview sheet

	Hospital admission	Hospital discharge	30-90 days post inclusion
Patient history			
Demographic data	x		
Pneumonia symptoms	x		
Co-morbidity	x		
Recent antibiotic use	x		
Physical examination			
Vital signs at emergency department	x		
Pneumonia scores	x		
Diagnostics			
Laboratory results at emergency department	x		
Chest radiograph at emergency department	x		
Microbiology			
Pneumococcal urine antigen test		x	
Legionella urine antigen test		x	
Sputum cultures		x	
Blood cultures		x	
Antibiotic stewardship			
Antibiotic use		x	
Antibiotic team advise log	x	x	x
Reasons to deviate from advices	x	x	x
Follow-up			
30-day mortality			x
90-day mortality			x
Readmission in 30 days			x

4. STUDY POPULATION

4.1 Sample size calculation

The study was designed to show non-inferiority of 30-day mortality in the intervention group. We calculated the required sample size based upon a binary non-inferiority trial. The estimated 30-day mortality for CAP patients is 5,2%. We estimated that 290 CAP patients get admitted to each hospital per year. Approximately 41 patients will be excluded due to immunosuppression (CAP-START data). The intra-cluster correlation was estimated to be $4.5*10^{-7}$ (estimated from the Dutch CAP study CAP-START, where the ICC for 90-day mortality was $4.5*10^{-7}$). We calculated the required one-sided sample size corrected for the design effect calculated with 10 participating hospitals and a non-inferiority margin of 3%. We assumed that no hospitals had a pre-intervention adherence of >70%. The estimated required sample size is 2543, while we will include approximately 3735 patients with 10 hospitals.

The increase in penicillin use after a comparable stewardship intervention was shown to increase from 187,5 to 273,7 DDD/1000 patients days (16). Using an estimated standard deviation of 100, a power of 80% and an alpha of 0.025, the required sample size is 52 patients. If we estimate that the percentage of patients receiving 7 days of penicillin increases from 40% to 50% and the patients switching to penicillin after 2 days increases from 10% to 20%, the DDD/1000 patients/day increases from 1.7 to 2.31. Using an estimated standard deviation of 2, a power of 80% and an alpha of 0,025, the required sample size is 424 patients. These estimations indicate that the 30-day mortality is the limiting factor in the sample size calculation.

6. SAFETY ASSESSMENT

Not applicable as patients undergo standard of care.

7. STATISTICAL ANALYSIS

The primary analysis will be done as intention-to-treat. We will determine the baseline differences between patient groups. Standard descriptive statistics will be used to describe the continuous or categorical values. Comparison of continuous variables between groups will be done using the Student's t-test and the Mann-Whitney U test. Categorical values will be analyzed using the Chi-square test. No interim analysis will be conducted. The stepped wedge design will be analyzed with a time-varying random effects multilevel model. Incomplete data will be imputed whenever possible. The analysis will be conducted unadjusted and adjusted for possible confounding covariates, including PSI-scores and baseline variables with a p-value <0.1.

As it is unlikely that we will see an intervention effect in centers with already high protocol adherence, we will post-hoc exclude the centers with a pre-intervention protocol adherence of >70% for the primary analysis.
A sensitivity analysis will be performed to analyze whether patients included during the implementation period have different outcomes.

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

Patients will be treated as standard of care. The study will be conducted according to the principles of the declaration of Helsinki.

8.2 Recruitment and consent

Patient data will be recorded routinely to assess the quality of care. Patients are informed that data can be collected to routinely assess the quality of care. As the patients are not subject to any intervention, a consent procedure is not conducted.

8.3 Benefits and risks assessment, group relatedness

There is no increased risk associated with participation in the study as patients will continue to be treated as standard of care.

9. DATA MANAGEMENT

Source documents that will be used to obtain research data include the medical record of the patient, laboratory reports and microbiology reports. Data recorded from these source documents will be entered coded in a digital CRF. CRFs will be completed by members of the research team of the participating hospitals.
Patients included in the study will be given a fictive inclusion number based on entry number to the study. Data obtained will be pseudonimized to prevent direct linkage of patient data to individual patients. The key to link the patient data to individual patients will be safeguarded by the antibiotic stewardship team of the participating center. The coordinating investigators will not be able to trace back research data on an individual basis.
Recorded data will be stored on a secured data server from the Julius Center, UMC Utrecht. The CRF's will be monitored for adequate completion by the coordinating investigators. The first 5 CRF's will be monitored completely. Subsequently CRF's will be monitored in 10% of cases. More intensive monitoring will be conducted when deemed necessary.

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11. APPENDIX

Attachment 1: standardized feedback

1.

Advice from the Antibiotic Stewardship team:
The first choice antibiotic treatment for moderate severe CAP is penicillin (i.v. 6dd 1m IU) or amoxicillin (i.v. 4dd 1000mg)*
When there are no contra-indications, we advise to switch the antibiotic or perform a pneumococcal urine antigen test.
The advised stop date is dd-mm-yyyy**
On dd-mm-yyyy a switch to oral amoxicillin 3-4 dd 500-750 can be considered**.

* Under condition that the patient shows good clinical response within 48 hours and no legionella risk factors.

** Under condition that the patient shows good clinical response

2.

Advice from the Antibiotic Stewardship team:
The pneumococcal urine antigen test is positive.
When there are no contra-indications we advise to switch the antibiotic to penicillin ((i.v. 6dd 1m IU)*
The advised stop date is dd-mm-yyyy**
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CAP-PACT study:

Community-acquired pneumonia: increasing protocol adherence by antibiotic stewardship in a stepped wedge cluster-randomized trial

Community-acquired Pneumonia
PACT
Antibiotic Stewardship Intervention Program

Version 4, March 2016

PROTOCOL TITLE: Community-acquired pneumonia: increasing protocol adherence by antibiotic stewardship in a stepped wedge cluster-randomized trial

Protocol ID: 1
Short title: CAP-PACT
Version: 2
Date: 01-03-2016

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TABLE OF CONTENTS

SUMMARY

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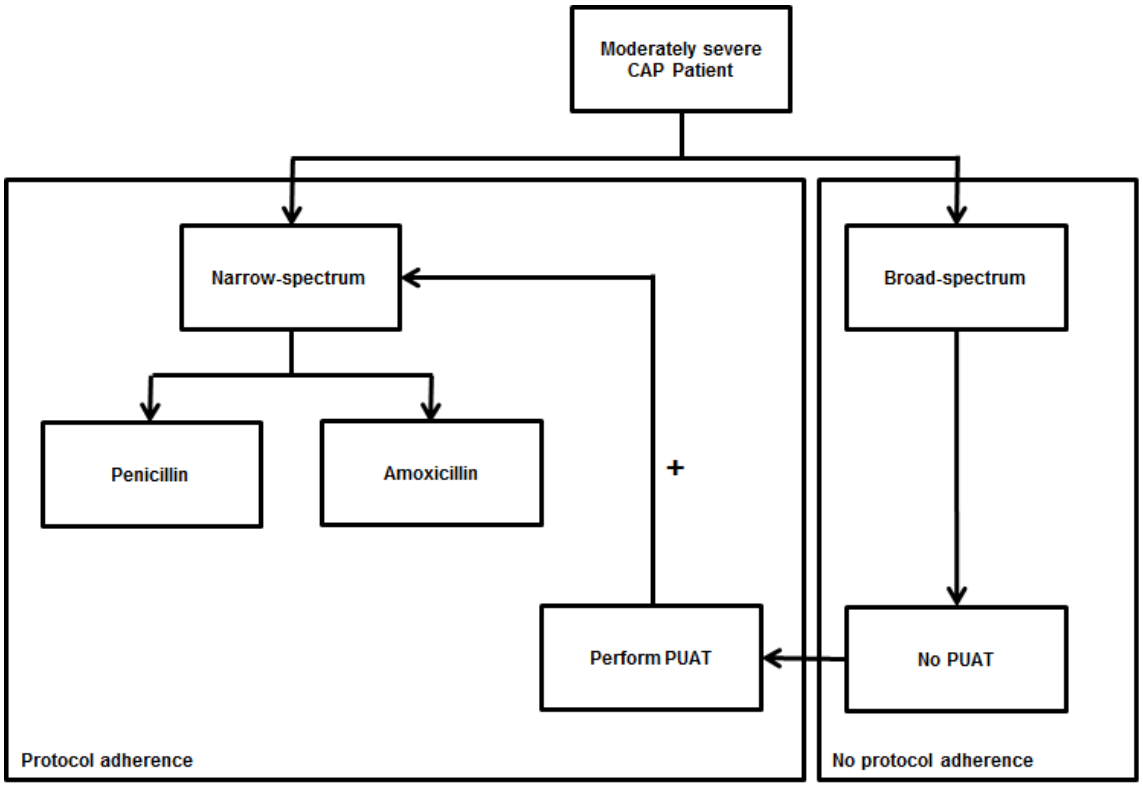

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3.1 Study design

The design will be a stepped wedge cluster randomized trial (Figure 2).

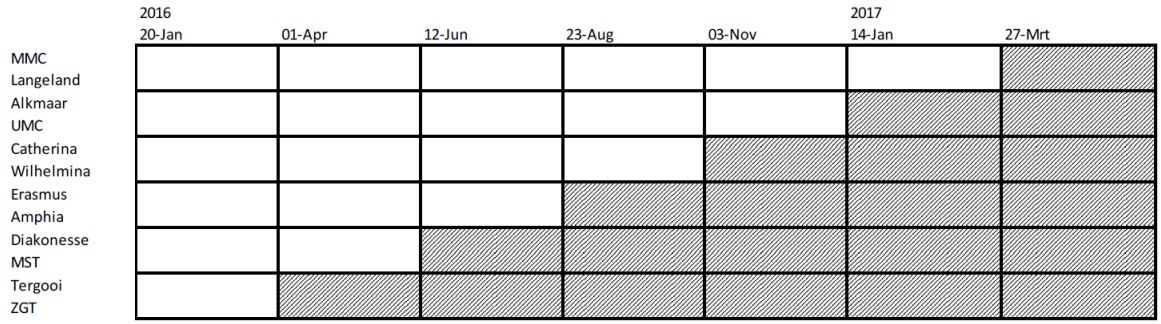

Figure 2. Stepped wedge design with a cluster size of 3 months with 10 participating hospitals.

In the stepped wedge design, hospitals will be randomly allocated to different times of intervention implementation. The stepped wedge design has several advantages. Firstly, all centers implement the Antibiotic Stewardship intervention, which is regarded as a quality improving program. It is logistically more feasible to implement the intervention bundle one at a time instead of all at once. In the stepped wedge design, the intervention effect can be

estimated from both between- and within- cluster comparison, resulting in more statistical power and a reduced required sample size (14). Lastly, but not least important for CAP, time-effects such as seasonal influences can be estimated and adjusted for by the design.

Hospitals will be randomly allocated to different times of intervention implementation. Randomization will be conducted electronically.

3.2 Inclusion procedure

Patients will be screened daily for inclusion eligibility. Initial screening will be conducted using the emergency department admission charts. Inclusion of the patients will be based on the working diagnosis of the emergency department physicians.

3.3 Inclusion criteria

Patients 18 years of age or older who get a admitted to a non-ICU department are eligible for inclusion.

3.4 Exclusion criteria

- Patients aged below 18 years
- Patients who immediately get admitted to the ICU
- Residence in a nursing home or long-term care facility in the last 14 days
- Patients hospitalized in an acute care hospital for two or more days in the last 14 days
- Patients with a history of Cystic Fibrosis
- Patients with immunodeficiency, defined as having one or more of the following criteria:
    - HIV infection with a last CD4 count of <300//µL
    - Cytotoxic chemotherapy or radiotherapy in the previous 3 months
    - Chronic hemodialysis > 3 months
    - History of receiving an organ or bone marrow transplant
    - Using immunosuppressive therapy, include corticosteroid treatment only when dosage is high (>0,5mg/kg/day) for a longer period of time (>14 days)

3.5 Intervention

The intervention will consist of a multifaceted antibiotic stewardship bundle formed on recommendations by the national and IDSA guidelines (17). The bundle consists of the following elements (Figure 3):

1. Education
2. Motivating opinion leaders
3. Adapting a pragmatic classification of disease severity
4. Prospective real-time audit and feedback

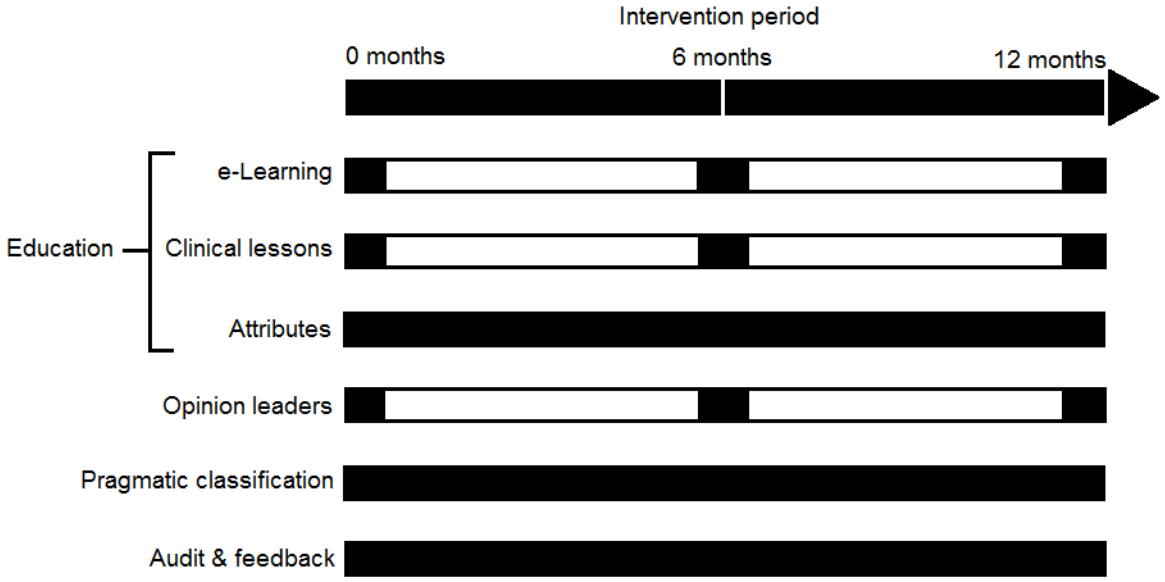

Figure 3. Timeline of intervention period with the corresponding intervals

1. Education

The education component of the intervention will be directed at physicians involved in the care of CAP patients and consist of:

1. e-Learning module
2. Clinical lessons
3. Distribution of educational attributes.

1.1 e-Learning module

We developed an e-Learning module where physicians will learn about the guideline through case-based reasoning. Response and attendance of the e-Learning will be monitored. The e-Learning will be repeated in 12 month intervals. New employees will be identified monthly and asked to participate.

1.2 Clinical lessons

Clinical lessons about the CAP guideline will be given in 6 months intervals. During these clinical lessons, physicians will be educated about the CAP guideline through case-based reasoning. In addition, previous performance as registered in the control period will be presented as feedback.

1.3 Educational attributes

Educational attributes, consisting of posters and pocket cards, will be distributed to all healthcare personnel involved in treating CAP patients at the start of the intervention. The purpose of these educational attributes will be to give clear and short overviews of how patients should be treated according to the guideline.

2. Adaptation of the pragmatic disease severity classification

The pragmatic classification is the easiest in use, most sparse in broad-spectrum antibiotic use and has the highest adherence in clinical practice (18). The intervention period will start with the promotion and implementation of the pragmatic disease severity classification. The pragmatic classification will be promoted in the other bundle components. Concomitant use of other disease severity scores is allowed to assess the general frailty of the patient. However, we strive to base the empiric treatment on the pragmatic disease severity classification.

3. Motivating opinion leaders

Opinion leaders of various departments will be identified and chosen by a local multidisciplinary panel at the start of the intervention period. These opinion leaders are the most likely to influence working behavior during routine clinical practice. Meetings will be scheduled with these opinion leaders in 6 months intervals. During these meetings, past performances and barriers that impede adherence will be discussed.

4. Audit and feedback

Prospective, real-time audit and feedback will be conducted by a local Antibiotic Stewardship team throughout the intervention period. The audit and feedback procedure will consist of daily evaluation of the antibiotic therapy of currently admitted CAP patients. The feedback to the caring physician will be done according to the following decision making flowchart (Figure 5):

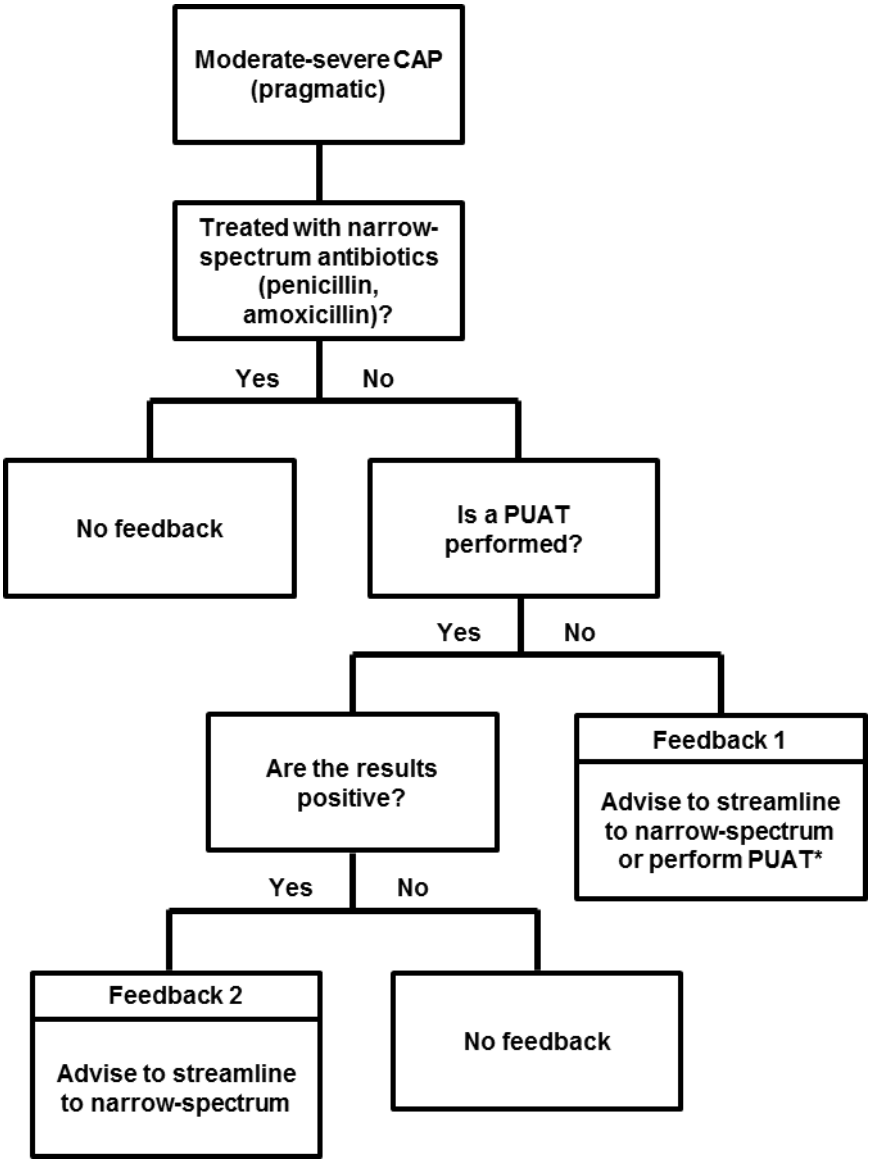

Figure 5. Decision making flowchart used in the audit and feedback procedure. Standardized feedback 1 and 2 can be found in the appendix.
**Pneumococcal urine antigen test*

The feedback will be done both personal by phone and written in the electronic patient file with standardized feedback responses (Attachment 1). If the hospital uses paper patient files, the recommendation will be printed and added to the patient file. Feedback will be given only once, with the exception of Feedback 1, where a Feedback 2 can follow after a positive pneumococcal urine antigen test (PUAT). It is important to note that the treating physician can always deviate from the given advice. Deviations with corresponding reasons will be registered in the case report form.

3.6 Data collection

Data will be entered in an electronic case report form (eCRF). On admission and inclusion the demographic data, presenting symptoms, co-morbidities, previous antibiotic use and the pneumonia severity scores will be recorded (Table 2). The Antibiotic Stewardship team advice log will be recorded when advices are given. At hospital discharge the antibiotic treatment received, culture results and feedback results will be recorded. The 30- and 90-day mortality will be registered 30 and 90 days after inclusion.

Table 2. Data collection overview sheet

	Hospital admission	Hospital discharge	30-90 days post inclusion
Patient history			
Demographic data	x		
Pneumonia symptoms	x		
Co-morbidity	x		
Recent antibiotic use	x		
Physical examination			
Vital signs at emergency department	x		
Pneumonia scores	x		
Diagnostics			
Laboratory results at emergency department	x		
Chest radiograph at emergency department	x		
Microbiology			
Pneumococcal urine antigen test		x	
Legionella urine antigen test		x	
Sputum cultures		x	
Blood cultures		x	
Antibiotic stewardship			
Antibiotic use		x	
Antibiotic team advise log	x	x	x
Reasons to deviate from advices	x	x	x
Follow-up			
30-day mortality			x
90-day mortality			x
Readmission in 30 days			x

4. STUDY POPULATION

4.1 Sample size calculation

The study was designed to show non-inferiority of 90-day mortality in the intervention group. We calculated the required sample size based upon a binary non-inferiority trial. The estimated 90-day mortality for CAP patients is 10%. We estimated that 290 CAP patients get admitted to each hospital per year. Approximately 41 patients will be excluded due to immunosuppression (CAP-START data). The intra-cluster correlation (ICC) was estimated to be $4.5*10^{-7}$ (CAP-START data, where the ICC for 90-day mortality was $4.5*10^{-7}$). Sample size calculation was performed using an one-sided α of 0,05 and to achieve 80% power with a non-inferiority margin of 3%. The sample size was corrected for the design effect. The sample size was calculated based on 12 participating hospitals with 6 steps. We assumed that no hospitals had a pre-intervention adherence of >70%. The estimated required sample size is 4464, while we will include approximately 4482 patients with 12 hospitals within 18 months.

The increase in penicillin use after a comparable stewardship intervention was shown to increase from 187,5 to 273,7 DDD/1000 patients days (16). Using an estimated standard deviation of 100, a power of 80% and an alpha of 0.025, the required sample size is 52 patients. If we estimate that the percentage of patients receiving 7 days of penicillin increases from 40% to 50% and the patients switching to penicillin after 2 days increases from 10% to 20%, the DDD/1000 patients/day increases from 1.7 to 2.31. Using an estimated standard deviation of 2, a power of 80% and an alpha of 0,025, the required sample size is 424 patients. These estimations indicate that the 90-day mortality is the limiting factor in the sample size calculation.

6. SAFETY ASSESSMENT

Not applicable as patients undergo standard of care.

7. STATISTICAL ANALYSIS

The primary analysis will be done as intention-to-treat. We will determine the baseline differences between patient groups. Standard descriptive statistics will be used to describe the continuous or categorical values. Comparison of continuous variables between groups will be done using the Student's t-test and the Mann-Whitney U test. Categorical values will be analyzed using the Chi-square test. No interim analysis will be conducted. The stepped wedge design will be analyzed with a mixed effects model with random effects for clusters and time. Incomplete data will be handled by multiple imputation whenever possible. The analysis will be conducted crude and adjusted for possible confounding covariates. Primary

analysis will be tested one-sided for a decrease in mortality. Secondary analysis to test two-sided for mortality will be performed.
As it is unlikely that we will see an intervention effect in centers with already high protocol adherence, we will post-hoc exclude the centers with a pre-intervention protocol adherence of >70% for the primary analysis. Stratified analyses per hospital will be conducted.
A sensitivity analysis will be performed to analyze whether patients included during the implementation period have different outcomes.

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

Patients will be treated as standard of care. The study will be conducted according to the principles of the declaration of Helsinki.

8.2 Recruitment and consent

Patient data will be recorded routinely to assess the quality of care. Patients are informed that data can be collected to routinely assess the quality of care. As the patients are not subject to any intervention, a consent procedure is not conducted.

8.3 Benefits and risks assessment, group relatedness

There is no increased risk associated with participation in the study as patients will continue to be treated as standard of care.

9. DATA MANAGEMENT

Source documents that will be used to obtain research data include the medical record of the patient, laboratory reports and microbiology reports. Data recorded from these source documents will be entered coded in a digital CRF. CRFs will be completed by members of the research team of the participating hospitals.
Patients included in the study will be given a fictive inclusion number based on entry number to the study. Data obtained will be pseudonimized to prevent direct linkage of patient data to individual patients. The key to link the patient data to individual patients will be safeguarded by the antibiotic stewardship team of the participating center. The coordinating investigators will not be able to trace back research data on an individual basis.
Recorded data will be stored on a secured data server from the Julius Center, UMC Utrecht.

The CRF's will be monitored for adequate completion by the coordinating investigators. The first 5 CRF's will be monitored completely. Subsequently CRF's will be monitored in 10% of cases. More intensive monitoring will be conducted when deemed necessary.

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11. APPENDIX

Attachment 1: standardized feedback

1. _____

Advice from the Antibiotic Stewardship team:
The first choice antibiotic treatment for moderate severe CAP is penicillin (i.v. 6dd 1m IU) or amoxicillin (i.v. 4dd 1000mg)*
When there are no contra-indications, we advise to switch the antibiotic or perform a pneumococcal urine antigen test.
The advised stop date is dd-mm-yyyy**
On dd-mm-yyyy a switch to oral amoxicillin 3-4 dd 500-750 can be considered**.

* Under condition that the patient shows good clinical response within 48 hours and no legionella risk factors.

** Under condition that the patient shows good clinical response

2. _____

Advice from the Antibiotic Stewardship team:
The pneumococcal urine antigen test is positive.
When there are no contra-indications we advise to switch the antibiotic to penicillin ((i.v. 6dd 1m IU)*
The advised stop date is dd-mm-yyyy**
On dd-mm-yyyy a switch to oral amoxicillin 3-4 dd 500-750 can be considered**.

* Under condition that the patient shows good clinical response within 48 hours and no legionella risk factors.

** Under condition that the patient shows good clinical response

Summary of amendments made to the study protocol from 22-07-2015 to 01-03-2016

- Before study initiation and at the time of registration of the trial at clinicaltrials.gov (11-11-2015, NCT02604628) the protocol was amended and these changes were incorporated in the next version of the protocol at 01-03-2016.

    - 90-day mortality instead of 30-day mortality was selected as the co-primary safety outcome. This change was subsequently changed in the next version of the protocol at 01-03-2016. Accordingly, the sample size calculation was also altered. Reasons for changing to 90-day mortality were to keep the outcomes consistent with the previously performed CAP-START trial (https://www.nejm.org/doi/full/10.1056/nejmoa1406330) and the recognition that patients treated for CAP have increased mortality risks for a prolonged period of time (PMID: 10421277).

    - ICU-admissions were included as secondary outcome.

    - Removed the exclusion criteria: "Patients where the suspected pathogen of the CAP is not treated with penicillin or amoxicillin (i.e. *Pneumocystis jiroveci*. Tuberculosis, etc.)". This exclusion criteria was removed because in clinical practice it may not always be possible to reliably determine whether patients were suspected of *Pneumocystis jiroveci* and Tuberculosis at the time that empiric antibiotics need to be started.

- Added details of the principal investigators of the participating centers.

- Clarified the recommendations of the national CAP guideline in Table 1 to include first-choice and second-choice treatment recommendations for both mild CAP, moderate-severe CAP and severe CAP.

- Figure 2 of the randomisation scheme was changed to include the details of hospital names.

- In the section describing the inclusion procedure the sentence: "Patients who get admitted to the internal medicine, geriatric or pulmonary department will be further evaluated." was removed because of redundancy.

- Rephrased the statistical analysis to better reflect the correct terminology. Time-varying random effects multilevel model was changed to mixed effects model with random effects for clusters and time. Imputed was changed to multiple imputation. Removed the sentence to select confounding variables based on a p-value <0.1 because this is statistically incorrect. The detailed method to account for confounders and the detailed statistical analysis plan was published separately before the database lock.

Statistical analysis plan CAP-PACT trial

06-07-2018

SUMMARY

The primary aim of the CAP-PACT trial is to demonstrate the safety and effectiveness of the antibiotic stewardship intervention to decrease the use of broad-spectrum antibiotics. The study has two co-primary outcomes: effectiveness is determined by broad-spectrum antibiotic use in days of therapy (DOT) and safety is determined by 90-day mortality. The analysis on antibiotic use will be a superiority analysis (to demonstrate a reduction in broad-spectrum antibiotic use) and the analysis on clinical outcome will be a non-inferiority analysis (non-inferiority in 90-day mortality). Three of the twelve hospitals dropped out from the study before the intervention was introduced. Two because the principal investigator left the hospital and no suitable replacement was available, and one because of insufficient patient recruitment. These hospitals will not be included in the data analysis. From the remaining centres, the data analysis will be performed on all patients included from 01-Nov-2015 till 01-Nov-2017, irrespective of the compliance to the stewardship intervention. The detailed statistical analysis plan has been established prior to database lock.

The primary analysis will be performed on patients with a clinical diagnosis of community-acquired pneumonia (CAP), with a sensitivity analysis in patients with radiologically confirmed CAP. Missing data will be handled by multiple imputation. Separate models will be fitted per endpoint. Adjusted models are corrected for the confounders: age, gender, PSI-score, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment. All models will be mixed effects regression models with a random intercept, a random effect per hospital, and time as a fixed linear effect. All models will be checked for cluster autocorrelation.

The models used for the statistical analysis are as follows:

Co-primary outcomes:

90-day mortality:

All analyses will be performed as mixed effects logistic regression models, both crude and adjusted

- Intention-to-treat (primary analysis):
  - Reported as risk differences as described by Kleinman and Norton (Health Serv Res 2009 Feb;44(1):288-302).
  - Test for non-inferiority: the upper limit of the 90% CI of the estimated absolute risk difference should not be more than 3%.
- As-treated (secondary analysis):

        - Determinant: empirical treatment with narrow-spectrum antibiotics versus broad-spectrum antibiotics
        - Reported as risk differences with corresponding 90% CI and test for non-inferiority (as ITT)
    - Complier Average Causal Effect (CACE) (secondary analysis)
        - As described by Greenland (Int J Epidemiol 2000; 29: 722–9.)
        - Randomisation will be used as an instrumental variable
        - Reported as risk differences with corresponding 90% CI

<u>Broad-spectrum days of therapy (DOT)</u>

Amoxicillin, penicillin and doxycycline are considered narrow-spectrum, other antibiotics are considered broad-spectrum antibiotics. Dual therapy with two broad-spectrum antibiotics will be considered as one broad-spectrum DOT, with a sensitivity analysis considering them as two broad-spectrum DOTs.

- Intention-to-treat (primary analysis):
    - Mixed effects Poisson regression models with broad-spectrum DOTs per patient as outcome

Secondary outcomes:

- 30-day mortality: as with 90-day mortality.
- Length of hospital stay: mixed effects cox regression model with in-hospital mortality as competing endpoint
- ICU admissions: mixed effects logistic regression model
- Readmissions: mixed effects logistic regression model
- Antibiotic switches: proportion estimated with mixed effects logistic regression models, time till switch estimated with mixed effects cox regression models

INTRODUCTION

This document describes the statistical analysis to determine the effect of an antimicrobial stewardship intervention on broad-spectrum antibiotic use and clinical outcome. The primary aim of the CAP-PACT trial is to demonstrate the safety and effectiveness of the antibiotic stewardship intervention to decrease the use of broad-spectrum antibiotics. The CAP-PACT trial is a stepped wedge cluster randomised trial. The implemented stewardship intervention consisted of (1) education, (2) audit and feedback, and (3) motivation of opinion leaders. The study has two co-primary outcomes: effectiveness is determined by broad-spectrum antibiotic use in days of therapy (DOT) and safety is determined by 90-day mortality. The analysis on antibiotic use will be a superiority analysis (to demonstrate a reduction in broad-spectrum antibiotic use) and the analysis on clinical outcome will be a non-inferiority analysis (non-inferiority in 90-day mortality). Three of the twelve hospitals dropped out from the study before the intervention was introduced. Two because the principal investigator left the hospital and no suitable replacement was available, and one because of insufficient patient recruitment. These hospitals will not be included in the data analysis. From the remaining centres, the data analysis will be performed on all patients included from 01-Nov-2015 till 01-Nov-2017, irrespective of the compliance to the stewardship intervention. The primary analysis will be performed on patients with a clinical diagnosis of community-acquired pneumonia (CAP). A sensitivity analysis will be performed in patients with radiologically confirmed CAP. All confounders used on the models are selected based on their theoretic associations with the outcome and will be added to the model without testing their distribution in the baseline and intervention periods.

Missing data, including outcomes, will be imputed by multiple imputation, with the exception of data on respiratory rate, heart rate, and confusion at admission; the values for these variables were assumed to be normal when data were missing. As a sensitivity analysis, a complete case analysis will be performed.

The detailed statistical analysis plan has been established prior to database lock.

OVERVIEW

DESCRIPTIVE STATISTICS

- Inclusion flowchart
- A baseline table comparing patients included in the control period to patients in the intervention period
- Process measures of the stewardship intervention
- Kaplan Meier curves of 90-day survival
- Visual representation of outcomes over time per hospital will be provided as recommended by Haines and Hemming (2018), example:

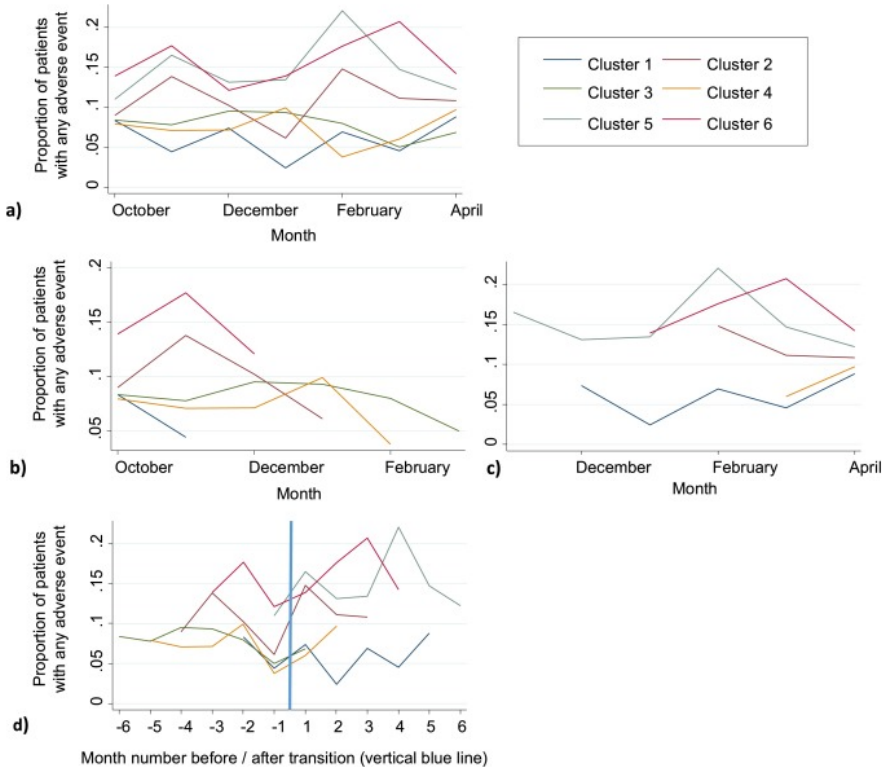

Figure 3

Line graphs based upon: a) whole trial data using calendar time; b) control period data using calendar time; c) intervention period data using calendar time; and d) whole trial data using time relative to the transition period.

Haines TP, Hemming K. Stepped-wedge cluster-randomised trials: level of evidence, feasibility and reporting. J Physiother. 2018 Jan;64(1):63-66. doi: 10.1016/j.jphys.2017.11.008. Epub 2017 Dec 27.

PRIMARY OUTCOMES

Clinical outcome (90-day mortality)

The primary analysis will be conducted according to intention-to-treat (ITT). In addition, we will perform an as-treated (AT) analysis and a Complier Average Causal Effect (CACE) analysis.

1. *Intention-to-treat (ITT) analysis*

In the ITT analysis, patients included in the intervention period will be compared to patient in the control period.

1a. 90-day mortality ITT crude

- Mixed effects logistic regression model, outcome: 90-day all-cause mortality (binary)
- Random intercept and random effect per hospital
- Time as fixed linear effect
- Determinant: intervention period versus control period
- Cluster autocorrelation will be checked by visually inspecting residuals
    - If cluster autocorrelation is present, an appropriate method for correction will be chosen based on model fit as determined by AIC
- To estimate risk differences from the logistic regression model, we will use a technique described by Kleinman and Norton (Health Serv Res 2009 Feb;44(1):288-302).
- Outcomes will be reported as risk differences with corresponding 90% CI (i.e. a one-sided alpha of 0.05)
- Test for non-inferiority: the upper limit of the 90% CI of the estimated absolute risk difference should not be more than 3%

1b. 90-day mortality ITT adjusted

- As (1a), with:
- Adjustment for confounding co-variates: age, gender, PSI-score, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment

2. *As-treated (AT) analysis*

In the AT analysis, patients receiving narrow-spectrum antibiotics (amoxicillin, penicillin, doxycycline) will be compared to patients receiving broad-spectrum antibiotics (all other antibiotics).

2a. 90-day mortality AT crude

- As (1a), with:
- Determinant: empirical treatment with narrow-spectrum antibiotics versus broad-spectrum antibiotics. Empirical treatment is defined as all antibiotic therapy given on the day of admission.
    - Narrow-spectrum antibiotics include:
        - Amoxicillin, penicillin, doxycyclin
    - Broad-spectrum antibiotics include:
        - Regiments including any of the other antibiotics

2b. Mortality AT adjusted

- As (2a), with:
- Adjustment for confounding co-variates: age, gender, PSI-score, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment, and controlled for control/intervention period

3. *Complier Average Causal Effect (CACE) / instrumental variable analysis*

The Complier Average Causal Effect (CACE) analysis can be used to adjust for non-compliance in a randomised controlled trial. In the CACE analysis, the effect of empirical treatment with narrow-spectrum versus broad-spectrum on mortality is estimated if all patients in the group with equipoise (i.e. in patients eligible to be treated with narrow-spectrum or broad-spectrum antibiotics) were empirically treated with narrow-spectrum or broad-spectrum antibiotics, i.e. 100% receiving broad-spectrum antibiotics in the control period and 100% receiving narrow-spectrum antibiotics in the intervention period.

3a. Mortality CACE crude

- As (1a), with:
- Randomisation will be used as an instrumental variable
- CACE analysis will be performed by dividing the ITT effect by the difference in the observed probabilities of receiving narrow-spectrum antibiotics between the two treatment allocation groups, as described by Greenland S. An introduction to instrumental variables for epidemiologists. Int J Epidemiol 2000; 29: 722–9.

- As the study was not designed to be powered for a CACE analysis, outcomes will be reported as risk differences with corresponding 95% CI without a formal non-inferiority analysis

3a. Mortality CACE adjusted

- As (3a), with:
- Adjustment for confounding co-variates: age, gender, PSI-score, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment

Antibiotic use (days of therapy (DOT))

Antibiotic use will be classified as broad-spectrum and narrow-spectrum median DOTs per patient. We will not standardize the DOT per patient days because the intervention can possibly affect the length of stay on patients. This can be considered a pragmatic effect of the intervention, which we want to measure, and not correct for. The primary outcome will be broad-spectrum DOTs.

Days that patients receive narrow-spectrum antibiotics (amoxicillin, penicillin, doxycycline) are defined as narrow-spectrum DOTs, and days that patients receive broad-spectrum antibiotics (any other antibiotic regimen) are defined as broad-spectrum DOTs. In the primary analysis, dual therapy will be counted one DOT (i.e. patients receiving combination therapy with a narrow-spectrum antibiotic and a broad-spectrum antibiotic will be counted as one broad-spectrum DOT, and patients receiving combination therapy with two broad-spectrum antibiotics will also be counted as one broad-spectrum DOT). In a sensitivity analysis, dual therapy will be counted as two DOTs. Both in-hospital and post-discharge antibiotic use will be included in the analysis of DOTs. Narrow-spectrum DOTs will be analysed similar to broad-spectrum DOTS.

4a. Broad-spectrum DOT, ITT crude

- Mixed effects Poisson regression model, outcome: broad-spectrum DOT (count data)
    - The assumptions for Poisson regression will be checked. In case of over or underdispersion, a negative binomial distribution will be used.
- Random intercept and random effect per hospital
- Time as fixed linear effect
    - As a sensitivity analysis: slope change after intervention will be determined
- Cluster autocorrelation will be checked by visually inspecting residuals
    - If cluster autocorrelation is present, an appropriate method for correction will be chosen based on model fit as determined by AIC
- Determinant: intervention period versus control period
- Outcomes will be reported as the median difference in broad-spectrum DOT per patient with corresponding 95% confidence intervals

4a. Broad-spectrum DOT, ITT adjusted

- As (4a), with:
- Adjustment for confounding co-variates: age, gender, PSI-score, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment

SECONDARY OUTCOMES

30-day mortality

5a. 30-day mortality ITT crude

- As (1a)

5b. 30-day mortality ITT adjusted

- As (1b)

5c. 30-day mortality AT crude

- As (2a)

5d. 30-day mortality AT adjusted

- As (2b)

5e. 30-day mortality CACE crude

- As (3a)

5f. 30-day mortality CACE adjusted

- As (3b)

Length of stay

6a. Length of stay ITT Crude

- Survival analysis model (Fine and Gray), outcome: time to discharge alive
    - Competing endpoint: in-hospital mortality
- Random intercept and random effect per hospital
- Time as fixed linear effect
- Cluster autocorrelation will be checked by visually inspecting residuals
    - If cluster autocorrelation is present, an appropriate method for correction will be chosen based on model fit as determined by AIC

- Determinant: intervention period versus control period
- Outcomes will be reported as hazard ratio's with corresponding 95% confidence intervals

6b. Length of stay ITT adjusted

- As (6a), with:
- Adjustment for confounding co-variates: age, gender, PSI-score, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment

ICU admissions

7a. ICU admissions ITT Crude

- Mixed effects logistic regression model, outcome: ICU admission (binary)
- Random intercept and random effect per hospital
- Time as fixed linear effect
- Cluster autocorrelation will be checked by visually inspecting residuals
    - If cluster autocorrelation is present, an appropriate method for correction will be chosen based on model fit as determined by AIC
- Determinant: intervention period versus control period
- Outcomes will be reported as Odds ratio's with corresponding 95% confidence intervals

7b. ICU admissions ITT Adjusted

- As (7a), with:
- Adjustment for confounding co-variates: age, gender, PSI-score, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment

Readmissions (30-day)

8a. Readmissions ITT Crude

- Mixed effects logistic regression model, outcome: readmissions within 30 days of hospital admission (binary)
- Random intercept and random effect per hospital
- Time as fixed linear effect
- Cluster autocorrelation will be checked by visually inspecting residuals
    - If cluster autocorrelation is present, an appropriate method for correction will be chosen based on model fit as determined by AIC

- Determinant: intervention period versus control period
- Outcomes will be reported as Odds ratio's with corresponding 95% confidence intervals

8b. Readmissions ITT Adjusted

- As (8a), with:
- Adjustment for confounding co-variates: PSI-score, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment

Antibiotic switches

Antibiotic switches will be described as (1) switches from broad-spectrum to narrow-spectrum antibiotics, (2) switches from narrow-spectrum to broad-spectrum antibiotics, (3) switches from intravenous to oral antibiotics, (4) switches from oral to intravenous and intravenous to oral antibiotics. Descriptive statistics will be used to describe the proportion switched and median time till switch with corresponding IQR. All analyses will be performed to describe both the proportion of patients switches as well as the time till switch.

9a. Proportion of antibiotic switches ITT Crude

- Mixed effects logistic regression model, outcome: antibiotic switch (binary)
- Random intercept and random effect per hospital
- Time as fixed linear effect
- Cluster autocorrelation will be checked by visually inspecting residuals
    - If cluster autocorrelation is present, an appropriate method for correction will be chosen based on model fit as determined by AIC
- Determinant: intervention period versus control period
- Outcomes will be reported as Odds ratio's with corresponding 95% confidence intervals

9b. Proportion of antibiotic switches ITT Adjusted

- As (9a), with:
- Adjustment for confounding co-variates: age, gender, PSI-score, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment

10a. Time till antibiotic switch ITT Crude

- Mixed effects cox regression model, outcome: time till antibiotic switch (continuous)
    - Competing endpoint: mortality
- Random intercept and random effect per hospital

- Time as fixed linear effect
- Cluster autocorrelation will be checked by visually inspecting residuals
    - If cluster autocorrelation is present, an appropriate method for correction will be chosen
- Determinant: intervention period versus control period
- Outcomes will be reported as Rate ratio's with corresponding 95% confidence intervals

10b. Time till antibiotic switch ITT Adjusted

- As (10a), with:
- Adjustment for confounding co-variates: age, gender, PSI-score, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment