UMC Utrecht

Cost-effectiveness of antibiotic treatment of community-acquired pneumonia: a cluster-randomized, multi-center, cross-over trial of 3 recommended treatment strategies

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ZonMw

CAP START

University Medical Center Utrecht

(potentiële) belangenverstrengeling	zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
• Sponsoring of onderzoeksgeld	• Pfizer (vaccins) • ZonMw

Antibiotica voor de behandeling van CAP (1)

- Keuze obv risico stratificatie
- 3 classificatiesystemen (zonder voorkeur)

Risk class	Pragmatic	PSI-score	CURB-65
Mild CAP	Ambulante behandeling	1-2	0-1
Moderate-severe CAP	Ziekenhuis opname (niet-IC)	3-4	2
Severe CAP	Opname in IC	5	3+

- Voor moderate-severe CAP
  - Beta-lactam monotherapy e.g. amoxicillin
  - Beta-lactam + macrolide e.g. penicillin + erythromycin
  - Fluoroquinolone monotherapy e.g. moxifloxacin

Antibiotica voor de behandeling van CAP (2)

- Geen doorslaggevend bewijs over beste therapie
- Mbt selectie van antibiotica resistentie:
  - **Beta-lactam monotherapy** is veiliger dan **Beta-lactam + macrolide** is veiliger dan **Fluoroquinolone monotherapy**
- Persoonlijke voorkeur van arts (of afgesproken beleid in ziekenhuis) bepaalt de strategie.

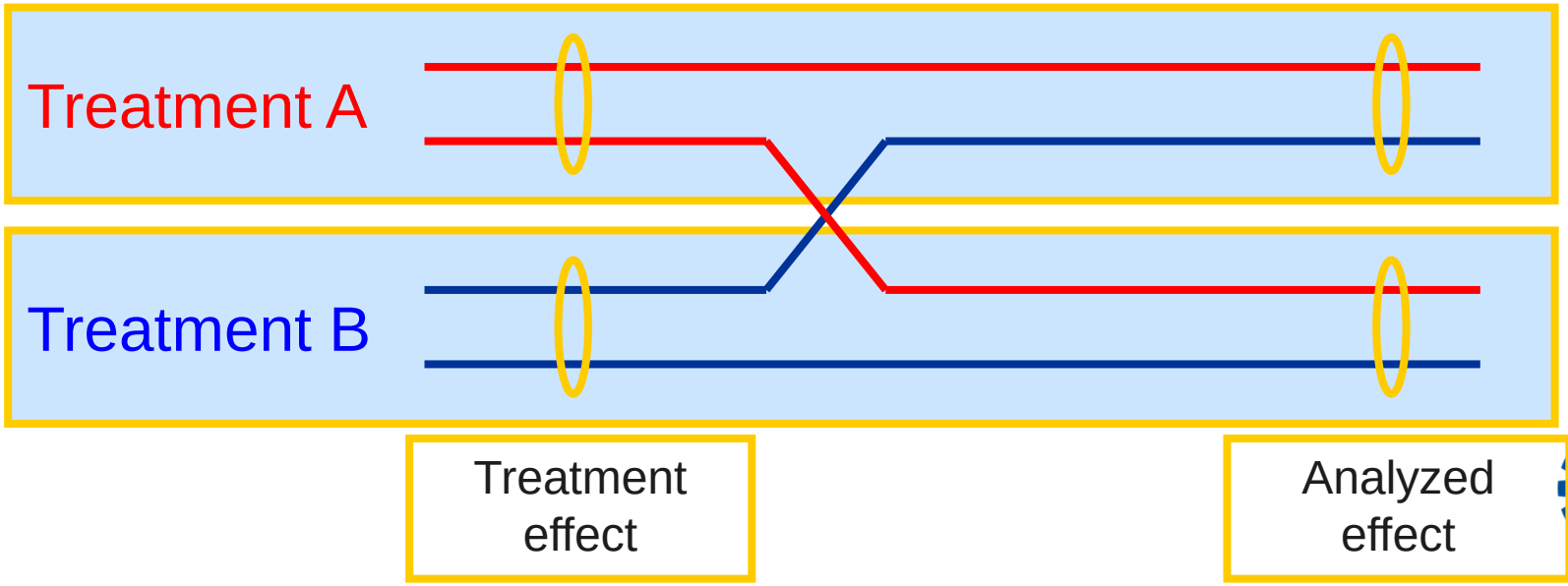
Beperkingen van observationeel onderzoek

- **Confounding by indication**
  - Keuze behandling beinvloed door de patient karakteristieken

- **Correctie door multivariate analyses is incompleet**
  - *Residuale confounding*

Beperkingen van Randomised Controlled Trials

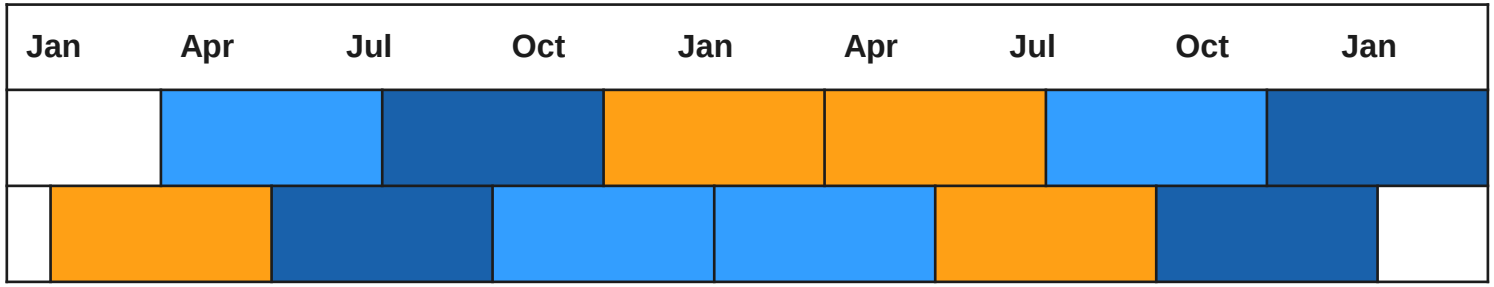
- **Selectie van patienten**
- **Misclassificatie van expositie**
  - Antibiotica moeten binnen 4 uur gegeven worden
  - Informed consent op SEH niet binnen 4 uur mogelijk
  - Randomisatie daarna → switch van antibioticum
  - Wsl is de initiele therapie het belangrijkst voor de uitkomst van de patient



Study design

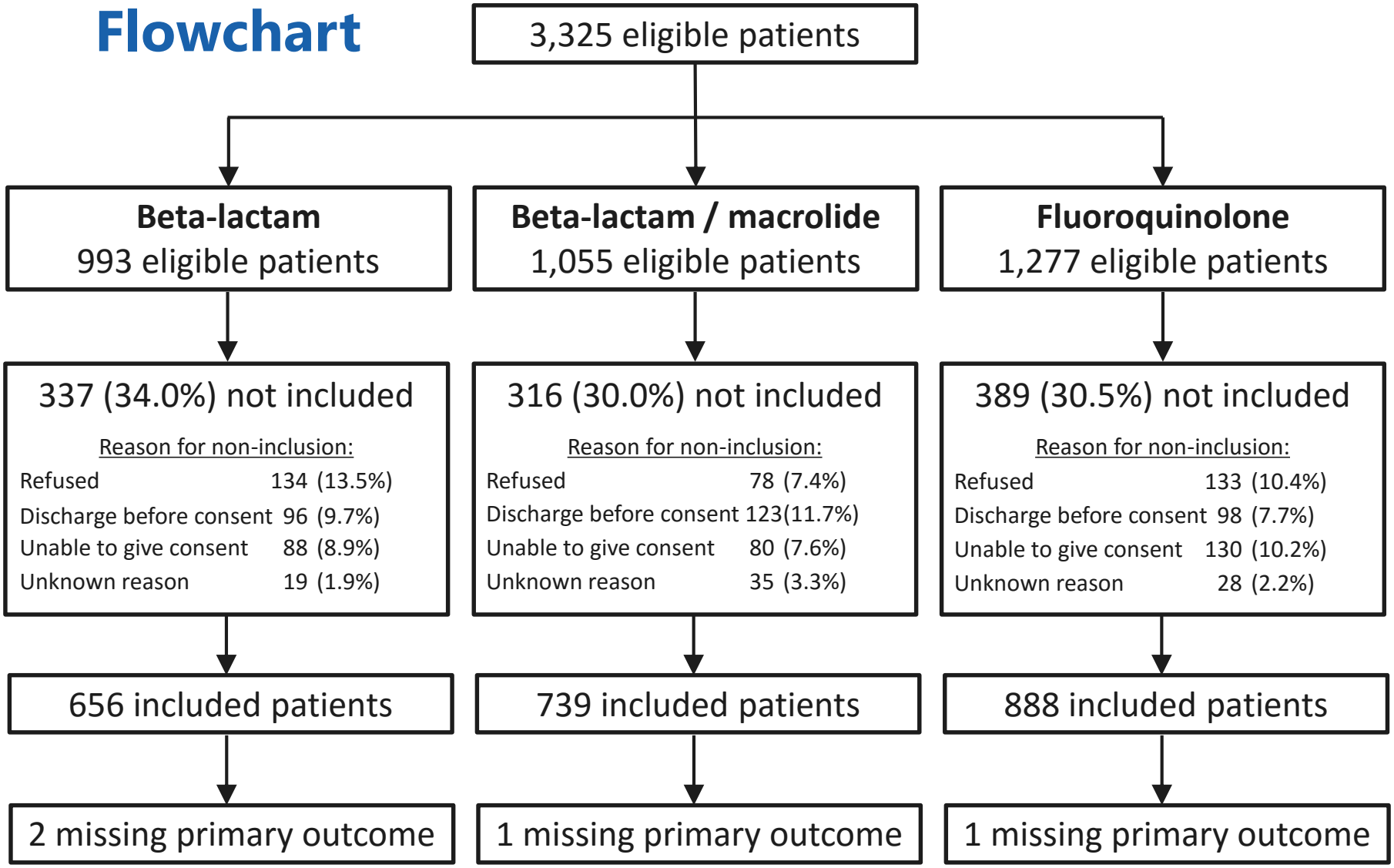
- Multicentre trial comparing empiric strategies for CAP patients admitted to non-ICU ward
- Antibiotic strategies
  - *Beta-lactam monotherapy (BL)*
  - *Beta-lactam + macrolide (BLM)*
  - *Fluoroquinolone monotherapy (FQL)*
- Outcome measures
  - Primary:
    - Non-inferiority of Beta-lactam strategy on day 90 mortality
  - Secondary:
    - Length of iv treatment
    - Length of stay
    - Complications

Treatment strategy comparison



- Empiric strategy randomised for each centre
  - Rotating every 4 months
  - Cluster randomization with cross-over
- Applies to all CAP-patients admitted to non-ICU ward
- Deviation for medical reason allowed
- Patient inclusion irrespective of antibiotic treatment

Flowchart


3,325 eligible patients
Beta-lactam
993 eligible patients
Beta-lactam / macrolide
1,055 eligible patients
Fluoroquinolone
1,277 eligible patients
337 (34.0%) not included
Reason for non-inclusion:
Refused 134 (13.5%)
Discharge before consent 96 (9.7%)
Unable to give consent 88 (8.9%)
Unknown reason 19 (1.9%)
316 (30.0%) not included
Reason for non-inclusion:
Refused 78 (7.4%)
Discharge before consent 123(11.7%)
Unable to give consent 80 (7.6%)
Unknown reason 35 (3.3%)
389 (30.5%) not included
Reason for non-inclusion:
Refused 133 (10.4%)
Discharge before consent 98 (7.7%)
Unable to give consent 130 (10.2%)
Unknown reason 28 (2.2%)
656 included patients
739 included patients
888 included patients
2 missing primary outcome
1 missing primary outcome
1 missing primary outcome

Baseline characteristics

	BL (n=656)	BLM (n=739)	FQL (n=888)
Age *	67.5 (15.5)	67.8 (15.7)	67.2 (15.9)
Male gender	381 (58.1%)	431 (58.3%)	505 (56.9%)
Hospitalised last year	271 (41.5%)	298 (41.3%)	351 (39.8%)
Cardiovascular disease	153 (23.3%)	154 (20.8%)	172 (19.4%)
COPD or Asthma	260 (39.6%)	281 (38.0%)	377 (42.5%)
Diabetes	118 (18.0%)	101 (13.7%)	161 (18.1%)
Malignancy	106 (16.2%)	124 (16.8%)	151 (17.0%)
Immunosuppressive therapy	59 (9.0%)	57 (7.7%)	93 (10.5%)
PSI score*	84.6 (29.0)	84.8 (27.8)	85.4 (28.5)
CURB-65 score ^	1 (1;2)	1 (1;2)	1 (1;2)
Radiologically confirmed CAP	506 (77.1%)	566 (76.6%)	665 (74.9%)

Legend: * Mean (SD) ^ Median (IQR)

Pathogens in X-ray proven CAP

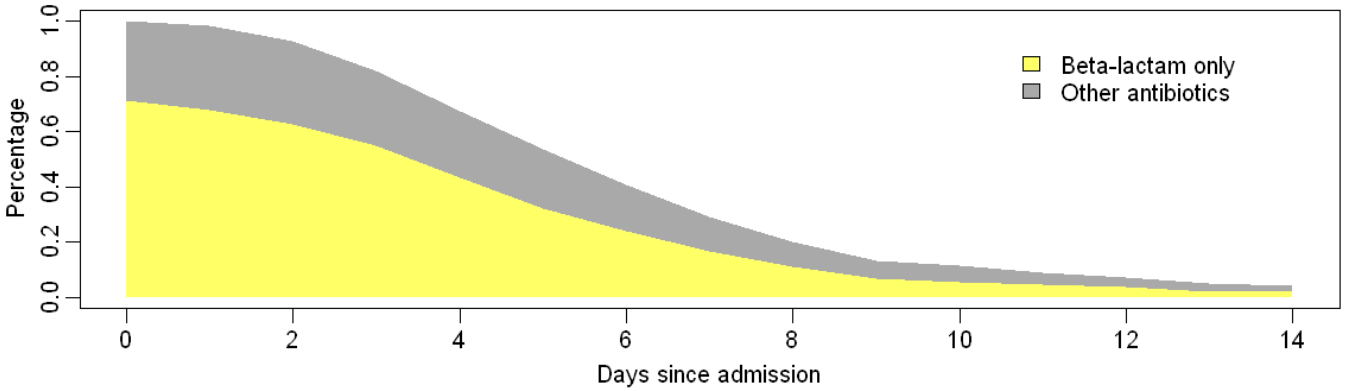
	BL proven	BL possible	BLM proven	BLM possible	FQL proven	FQL possible
Streptococcus pneumoniae	60 (11.9%)	16 (3.2%)	77 (13.6%)	15 (2.7%)	94 (14.1%)	20 (3.0%)
Haemophilus influenzae	1 (0.2%)	37 (7.3%)	3 (0.5%)	45 (8.0%)	2 (0.3%)	40 (6.0%)
Moraxella catarrhalis	-	6 (1.2%)	-	11 (1.9%)	-	7 (1.1%)
Staphylococcus aureus	2 (0.4%)	15 (3.0%)	2 (0.4%)	17 (3.0%)	4 (0.6%)	15 (2.3%)
Escherichia coli	1 (0.2%)	15 (3.0%)	5 (0.9%)	17 (3.0%)	3 (0.5%)	7 (1.1%)
Klebsiella pneumoniae	-	4 (0.8%)	1 (0.2%)	5 (0.9%)	-	5 (0.8%)
Pseudomonas aeruginosa	-	11 (2.2%)	-	16 (2.8%)	-	8 (1.2%)
Legionella pneumophila	6 (1.2%)	-	7 (1.2%)	-	2 (0.3%)	1 (0.2%)
Mycoplasma pneumoniae	-	7 (1.4%)	-	2 (0.4%)	-	12 (1.8%)
Other pathogens	4 (0.8%)	46 (9.1%)	4 (0.7%)	61 (10.8%)	11 (1.7%)	48 (7.2%)
No Pathogen	323 (63.8%)		342 (60.4%)		436 (65.6%)	

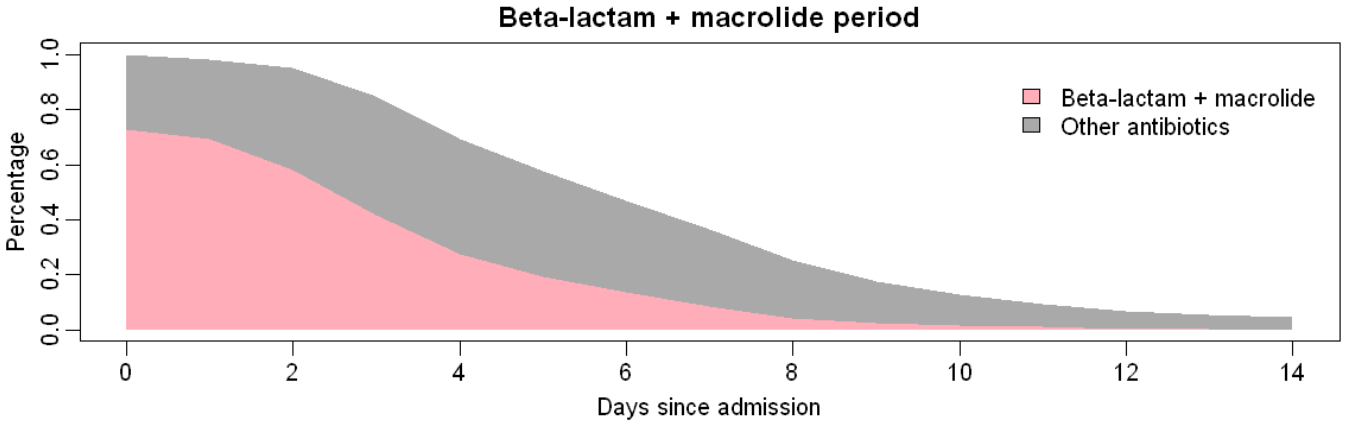
Protocol adherence

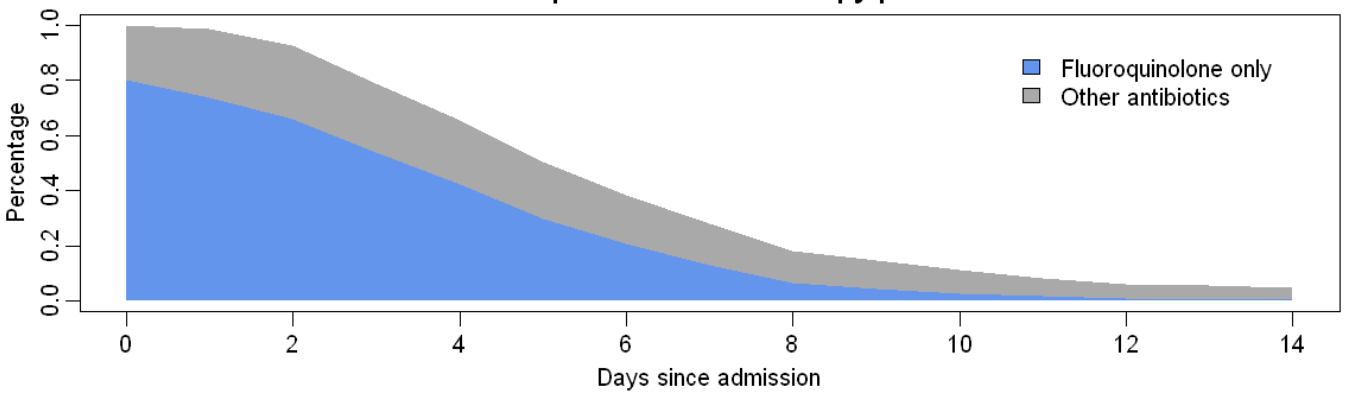
	BL (n=656)	BLM (n=739)	FQL (n=888)
Non-adherence	46 (7.0%)	89 (12.0%)	65 (7.3%)
Protocol adherence	610 (93.0%)	650 (88.0%)	823 (92.7%)
Treated per protocol	468 (71.3%)	538 (72.8%)	712 (80.2%)
Protocol adherent deviations			
Suspected pathogen	56 (8.5%)	11 (1.5%)	11 (1.2%)
Relating to pre-hospital antibiotics	27 (4.1%)	27 (3.7%)	23 (2.6%)
Contraindication	21 (3.2%)	29 (3.9%)	25 (2.8%)
Known colonization	17 (2.6%)	26 (3.5%)	23 (2.6%)
Other reasons	22 (3.4%)	22 (3.0%)	31 (3.5%)

Pr

	(n=888)
Non-adhe	7.3%)
Protocol a	(92.7%)
Treate	(80.2%)
Protoc	
Sus	1.2%)
Rela	2.6%)
Con	2.8%)
Kno	2.6%)
Oth	3.5%)

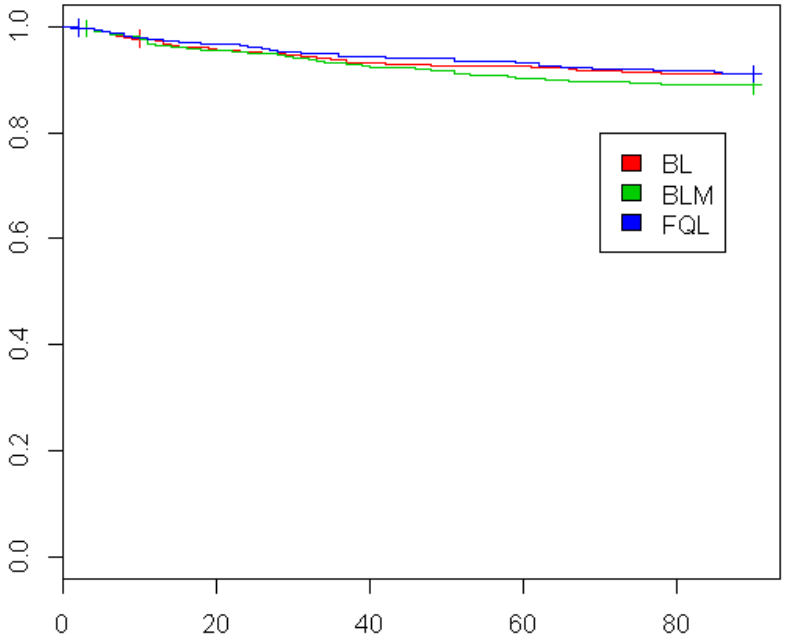




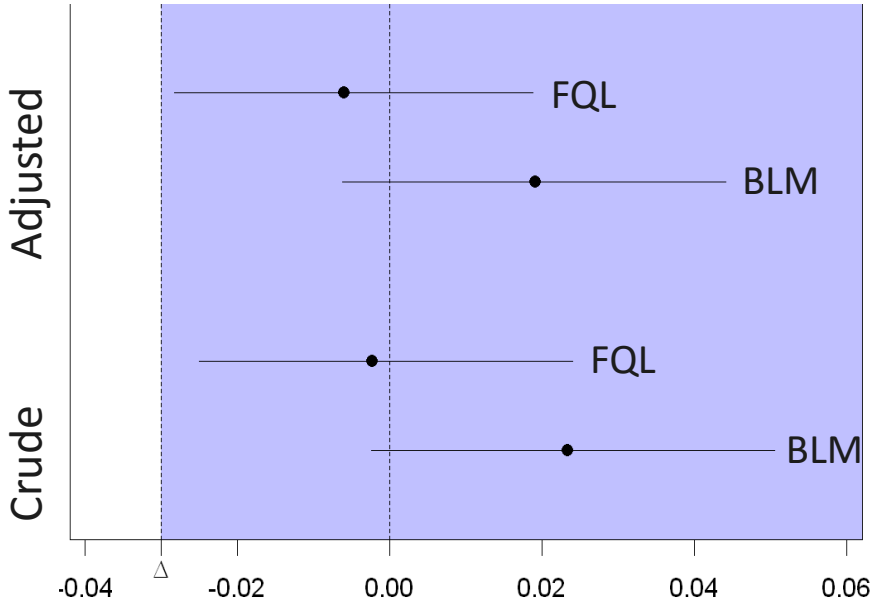


Primary outcome: day 90 mortality
Intention-to-treat analysis (ITT)

Survival curve



Risk difference



BL: 9.0 % (n=59)
BLM: 11.2% (n=83)
FQL: 8.8% (n=78)

Primary outcome: day 90 mortality

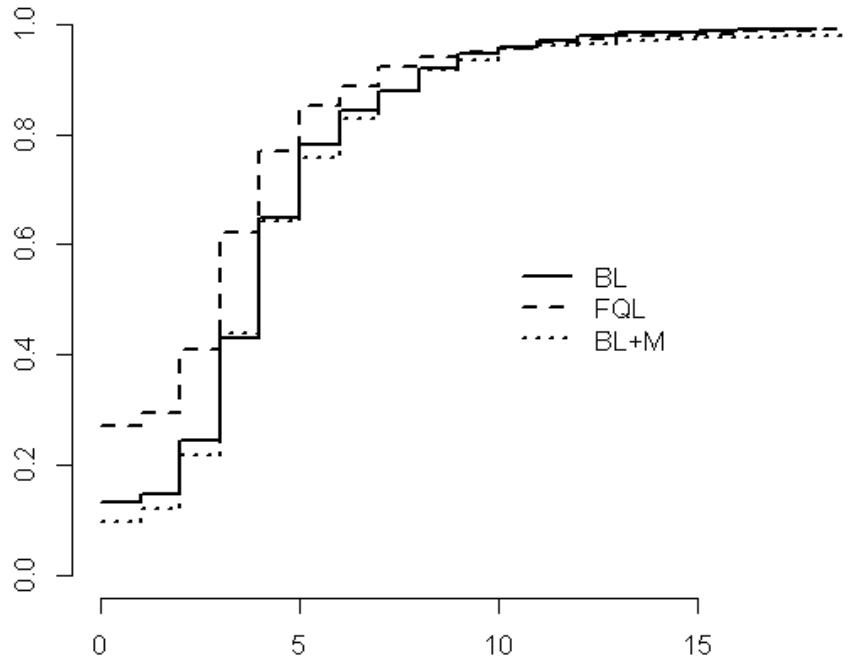
	N	BLM	FQL
All cases			
ITT crude	2279	2.3% (-0.2%;5.0%)	-0.2% (-2.5%;2.4%)
ITT adjusted	2279	1.9% (-0.6%;4.4%)	-0.6% (-2.8%;1.9%)
AA crude	1717	1.3% (-1.2%;4.9%)	-1.7% (-4.1%;1.1%)
AA adjusted	1717	2.1% (-0.5%;5.0%)	-0.4% (-2.7%;2.2%)
Radiologically proven CAP			
ITT crude	1733	2.9% (0.0%;6.1%)	-0.1% (-2.9%;2.8%)
ITT adjusted	1733	2.5% (-0.6%;5.2%)	-0.7% (-3.4%;1.8%)
AA crude	1309	1.8% (-1.6%;5.7%)	-2.2% (-5.3%;0.9%)
AA adjusted	1309	3.0% (-0.3%;6.2%)	-0.5% (-3.5%;2.4%)

ITT: intention-to-treat

AA: antibiotic adherent

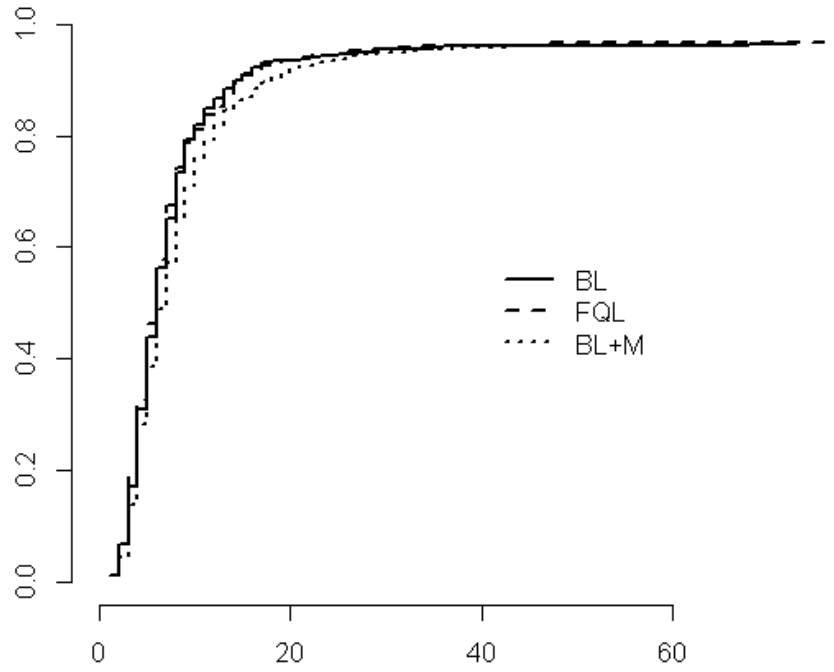
Time to oral treatment (ITT)

Outcome	BL	BLM	FQL
Median (IQR)	4 (3-5)	4 (3-5)	3 (0-4)
Hazard ratio's for iv-oral switch			
Crude	reference	0.95 (0.84 to 1.08)	1.28 (1.13 to 1.44)
Adjusted	reference	0.97 (0.86 to 1.09)	1.29 (1.15 to 1.46)

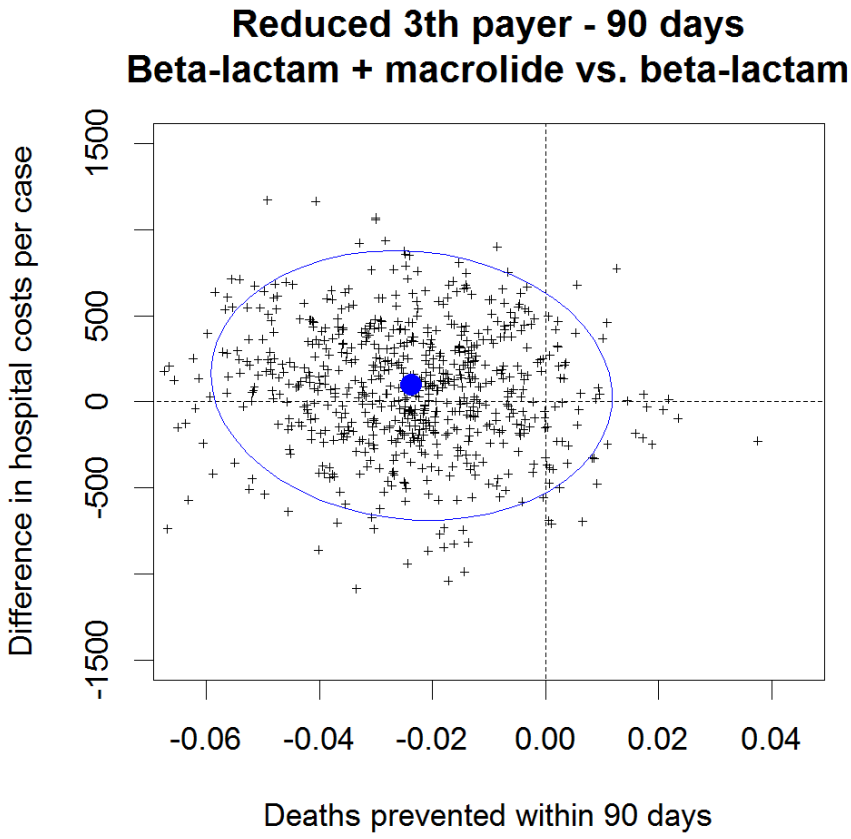


Length of stay (ITT)

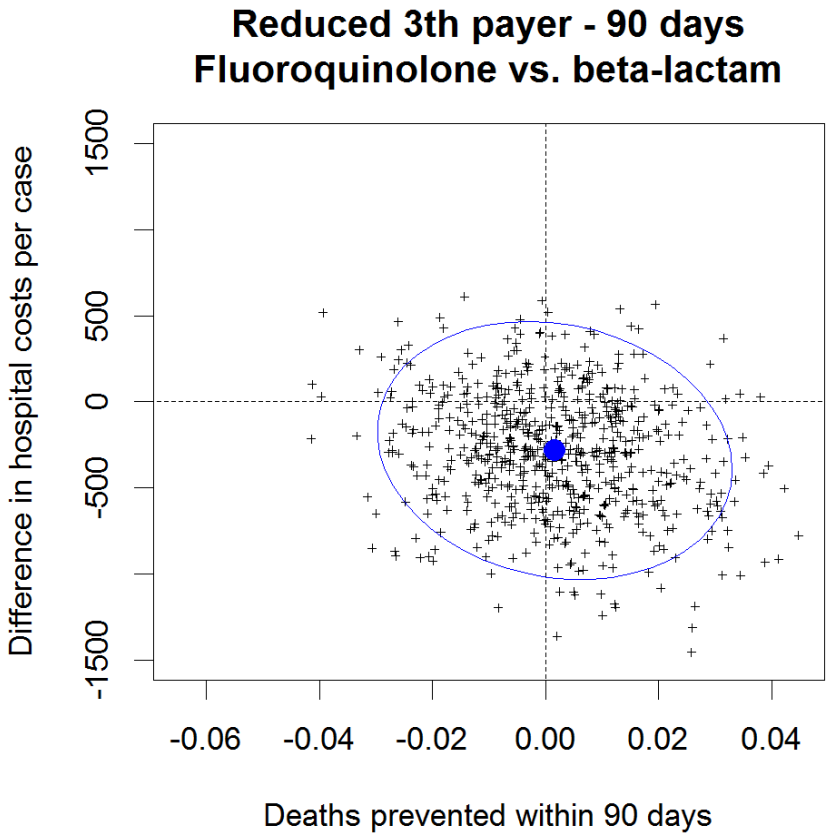
Outcome	BL	BLM	FQL
Median (IQR)	6 (4-8)	6 (4-10)	6 (4-8)
Hazard ratio's for discharge			
Crude	reference	0.86 (0.77 to 0.96)	1.03 (0.93 to 1.15)
Adjusted	reference	0.87 (0.78 to 0.97)	1.04 (0.94 to 1.16)



Results: Cost-effectiveness
Reduced 3th payer - 90 days



Δ costs: +106 (95%CI -697;+754)



Δ costs: -278 (95%CI -991;+396)

Conclusion

- Strategy of empiric beta-lactam monotherapy is non-inferior to strategies including atypical coverage in CAP patients admitted to non-ICU ward

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ORIGINAL ARTICLE

Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults

Douwe F. Postma, M.D., Cornelis H. van Werkhoven, M.D., Leontine J.R. van Elden, M.D., Ph.D., Steven F.T. Thijsen, M.D., Ph.D., Andy I.M. Hoepelman, M.D., Ph.D., Jan A.J.W. Kluytmans, M.D., Ph.D., Wim G. Boersma, M.D., Ph.D., Clara J. Compaijen, M.D., Eva van der Wall, M.D., Jan M. Prins, M.D., Ph.D., Jan J. Oosterheert, M.D., Ph.D., and Marc J.M. Bonten, M.D., Ph.D., for the CAP-START Study Group*

On behalf of the CAP-START study group

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