Introduction
Optimal empirical antibiotic treatment of adult patients hospitalized with clinically suspected community-acquired pneumonia (CAP) in non-ICU wards is unknown. We evaluated if a strategy of preferred initial treatment with Beta-lactam monotherapy (BL) is non-inferior to a strategy of Beta-lactam/macrolide combination (BLM) or a strategy of Fluoroquinolone monotherapy (FQL).

Methods
- Cluster-randomized cross-over trial in seven Dutch hospitals (figure 1)
- CAP patients admitted to a non-ICU ward
- Deviation from preferred antibiotics for medical reason allowed (strategy adherent population)
- Primary outcome: day-90 mortality (non-inferiority margin of 3% absolute difference) in intention-to-treat population
- Subgroup analysis of strategy adherent population
- Secondary outcomes: length of stay, time to oral treatment
- Mixed effects regression for cluster design

Antibiotic consumption
- Protocol compliance per arm is given in Figure 2.
- Main reason for deviation in the BL arm is suspicion of an atypical pathogen (53; 8.1%). Other reasons were similar between arms.
- Received antibiotics are summarized in figure 3.

Figure 2: Inclusion chart

Table: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>BL (N=656)</th>
<th>BLM (N=739)</th>
<th>FQL (N=888)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age *</td>
<td>68 (16)</td>
<td>68 (16)</td>
<td>67 (16)</td>
</tr>
<tr>
<td>Female gender</td>
<td>381 (58%)</td>
<td>431 (58%)</td>
<td>505 (57%)</td>
</tr>
<tr>
<td>Antibiotics before admission</td>
<td>219 (34%)</td>
<td>227 (32%)</td>
<td>303 (35%)</td>
</tr>
<tr>
<td>Influenza vaccination</td>
<td>453 (73%)</td>
<td>466 (67%)</td>
<td>572 (68%)</td>
</tr>
<tr>
<td>Pneumococcal vaccination</td>
<td>16 (3%)</td>
<td>18 (3%)</td>
<td>13 (2%)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>153 (23%)</td>
<td>154 (21%)</td>
<td>172 (19%)</td>
</tr>
<tr>
<td>COPD or Asthma</td>
<td>260 (40%)</td>
<td>281 (38%)</td>
<td>377 (43%)</td>
</tr>
<tr>
<td>Immunocompromized</td>
<td>145 (22%)</td>
<td>172 (23%)</td>
<td>210 (24%)</td>
</tr>
<tr>
<td>CURB-65 score *</td>
<td>1 (1.2)</td>
<td>1 (1.2)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Radiologically confirmed CAP</td>
<td>506 (77%)</td>
<td>566 (77%)</td>
<td>665 (75%)</td>
</tr>
</tbody>
</table>

Pathogens
- Blood cultures were performed in 1737 (76%), pneumococcal antigen test in 1797 (79%), Legionella antigen test in 1734 (76%), and sputum culture in 1043 (46%) patients.
- S. pneumoniae was the most frequent pathogen (282; 12.4%) followed by H. influenzae (128; 5.6%), L. pneumophila was detected in 16 patients (0.7%).

Primary outcome
- Day-90 mortality was 9.0% (n=59), 11.1% (n=82), and 8.8% (n=78) in BL, BLM, and FQL periods, respectively.
- Non-inferiority of BL was met for both arms (Figure 4) in intention-to-treat analysis and in a sensitivity analysis of strategy adherent patients.
- An unplanned, post-hoc analysis of patients receiving the preferred antibiotic, the antibiotic adherence analysis, also showed non-inferiority after adjustment for potential confounders.

Discussion
- In patients hospitalized with CAP, a strategy of preferred empirical treatment with BL was non-inferior to strategies with BLM or FQL, reducing atypical coverage by 46-52%.
- Although subgroup analyses of patients treated according to the preferred strategy or receiving the preferred antibiotics were biased through confounding by indication, estimates were similar as in the ITT analysis after adjustment for confounders.
- More eligible patients led to more inclusions in the FQL period due to seasonal variation. However, baseline characteristics and microbiology were comparable.
- These results may not be generalizable to regions with a considerably different microbiological etiology of CAP.

Conclusion
A strategy of preferred empirical treatment with BL for patients hospitalized to non-ICU wards with clinically suspected CAP is non-inferior to strategies of preferred empirical treatment with BLM or FQL.