Supportive care and antibiotics for severe pneumonia among hospitalized children (SEARCH)

A pragmatic randomized controlled trial
Outline

• Background to proposed trial
• Justification for SEARCH Trial
• SEARCH trial study population and design
Background to SEARCH Trial

Amoxicillin for Severe Pneumonia Pragmatic Trial

Child Health Evidence Week

Amoxicillin vs Benzyl penicillin for severe pneumonia

-2 Strongly Reject
-1 Neither Reject nor Support
0 Strongly Support
### Amoxicillin vs benzyl penicillin for indrawing pneumonia

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Treatment failure 48 hr (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>20/260 (7.7)</td>
</tr>
<tr>
<td>Benzyl penicillin</td>
<td>21/261 (8.0)</td>
</tr>
</tbody>
</table>

**Risk Difference**  
-0.3% (-5.0, 4.3)*  
(95% CI)

*Non-inferiority margin: 7%*
### 2016 Pneumonia Guidelines

<table>
<thead>
<tr>
<th>Severe pneumonia</th>
<th>Inpatient</th>
<th>Injectable penicillin + gentamicin + oxygen, feeds/fluid support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>Fast breathing (≥50/min if age 2-11 months; ≥40/min if age 12-59 months)</td>
<td>AND without signs of severe or very severe pneumonia</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Lower chest wall indrawing</td>
<td>AND without signs of very severe pneumonia</td>
</tr>
<tr>
<td>No Pneumonia</td>
<td>None of the signs of non-severe, severe or very severe pneumonia</td>
<td>Outpatient Oral amoxicillin</td>
</tr>
<tr>
<td></td>
<td>No antibiotics</td>
<td>Outpatient Oral amoxicillin</td>
</tr>
</tbody>
</table>

Ministry of Health
Republic of Kenya.
Basic Paediatric Protocols
February 2016
# 2016 Pneumonia Guidelines

<table>
<thead>
<tr>
<th>Severe Pneumonia</th>
<th>Any one of: cyanosis, grunting (infants), inability to drink, head nodding, altered consciousness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pneumonia</strong></td>
<td>Lower chest wall indrawing * AND without signs of very severe pneumonia *</td>
</tr>
<tr>
<td><strong>Pneumonia</strong></td>
<td>Fast breathing (RR≥50/min if age 2-11 months; ≥40/min if age 12-59 months) * * * AND without signs of severe or very severe pneumonia * * *</td>
</tr>
<tr>
<td><strong>No Pneumonia</strong></td>
<td>None of the signs of non-severe, severe or very severe pneumonia * * * * * * * *</td>
</tr>
</tbody>
</table>

- **Inpatient**
  - Injectable penicillin + gentamicin + oxygen, feeds/fluid support

- **Outpatient**
  - Oral amoxicillin

- **Outpatient**
  - No antibiotics

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*Ministry of Health
Republic of Kenya. Basic Paediatric Protocols
February 2016*
Rationale behind WHO pneumonia case management recommendations

Severe pneumonia

Non severe pneumonia

High mortality → Admit

Low mortality → Home care
Results: Mortality by WHO clinical severity category

Severe pneumonia

- 14.2%*
  - High mortality
  - Admit

Non severe pneumonia

- 2.7%**
  - Low mortality
  - Home care
Mortality by WHO clinical severity category

14.2%*

23.5%

7.4%
Why are children with pneumonia dying?

- Delayed care-seeking / referral
- Poor quality inpatient care
- Ineffective treatment
- Sub-optimal supportive care

Inpatient
Management of severe pneumonia

- Ineffective treatment
- Sub-optimal supportive care

- Antibiotics
- Fluids / feeds / respiratory support
SEARCH Trial

Children with severe pneumonia

Benzyl penicillin + gentamicin  IV amoxicillin-clav  Ceftriaxone  Nasogastric feeds  IV fluids

Mortality at Day 5  Social science  Health economics
SEARCH Trial

- 3x2 pragmatic factorial trial
- Sample: 4392 children in up to 12 sites
- Primary endpoint: mortality at Day 5 post-enrolment
- Secondary outcomes: length of hospitalisation, mortality at Day 30
- Other outcomes: cost effectiveness, social perceptions of caregivers and health workers towards the study treatments
Pragmatic versus explanatory RCTs

- **Explanatory trials**: undertaken in an idealized setting, to give the initiative under evaluation its best chance to demonstrate a beneficial effect.

- **Pragmatic trials**: undertaken in the “real world” with usual care. Intended to help support policy decisions on whether to deliver interventions.

**Pragmatic**
- High *external* validity
- Large sample size
- Lax eligibility criteria

**Explanatory**
- High *internal* validity
- Smaller sample size
- Stringent eligibility criteria
# Timeline

<table>
<thead>
<tr>
<th>Activity</th>
<th>Mar ’18</th>
<th>Jun ’18</th>
<th>Sep ’18</th>
<th>Dec ’18</th>
<th>2019</th>
<th>2020</th>
<th>Jun ’21</th>
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<tbody>
<tr>
<td>Ethical review</td>
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<td>Training/set up of sites</td>
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<td>Recruitment / data collection</td>
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<td>Interim analysis</td>
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<td>Study close out</td>
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<td>Analysis and reporting</td>
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Summary

• Local evidence from clinical trials can influence policy and clinical practice
• Mortality due to severe pneumonia is high even where implementation of treatment guidelines is good
• SEARCH is a pragmatic trial that seeks to compare management strategies for severe pneumonia:
  • first line antibiotics (xpen / gentamicin) versus ceftriaxone versus amoxiclav
  • IV fluids vs nasogastric fluids
• Recruitment to begin in Q1 2019