GLOBAL ANTIBIOTIC RESEARCH & DEVELOPMENT PARTNERSHIP

CO-AMOXICLAV
(AMOXICILLIN + CLAVULANATE)

Dr. Marie-Claude BOTTINEAU
Dr. Emmanuel BARON
## Summary of global estimates

*(CHERG 2013)*

### ~ 6.6 million deaths among children < 5 years old

<table>
<thead>
<tr>
<th>Disease</th>
<th>Percentage</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>18%</td>
<td>1.2 million</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10%</td>
<td>0.66 million</td>
</tr>
<tr>
<td>Malaria</td>
<td>7%</td>
<td>0.46 million</td>
</tr>
<tr>
<td>Complications of prematurity</td>
<td>14%</td>
<td>0.93 million</td>
</tr>
<tr>
<td>Complications caused by pregnancy</td>
<td>11%</td>
<td>0.73 million</td>
</tr>
<tr>
<td>Infections &amp; Meningitis</td>
<td>5%</td>
<td>0.33 million</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4%</td>
<td>0.27 million</td>
</tr>
</tbody>
</table>

### 64% (4.2 million) deaths due to infectious diseases

- **Pneumonia**: 18% (1.2 million)
- **Diarrhea**: 10% (0.66 million)
- **Malaria**: 7% (0.46 million)

### 43% (~ 3.1 million) of neonatal deaths

- **Complications of prematurity**: 14% (0.93 million)
- **Complications caused by pregnancy**: 11% (0.73 million)
- **Infections & Meningitis**: 5% (0.33 million)
- **Pneumonia**: 4% (0.27 million)
MSF Context / Beneficiaries (2014)  
*(Partial Data, underestimation)*

<table>
<thead>
<tr>
<th>CHILDREN UNDER 5</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Outpatient department</td>
<td>&gt; 2 M</td>
</tr>
<tr>
<td>Inpatient department</td>
<td>&gt; 200 000</td>
</tr>
<tr>
<td>Global Acute Malnutrition</td>
<td>&gt; 300 000</td>
</tr>
</tbody>
</table>
# MSF Co-Amoxiclav Supply (2014)

<table>
<thead>
<tr>
<th>Ratio 4:1</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>Suspension</td>
<td>31 361 (1.2%)</td>
<td></td>
</tr>
<tr>
<td>Non breakable tablets</td>
<td>656 012 (24.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>687 373 (25.6%)</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ratio 7:8:1</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspension</td>
<td>40 405 (1.5%)</td>
<td></td>
</tr>
<tr>
<td>Non-breakable tablets</td>
<td>1 962 283 (72.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>2 002 688 (74.4%)</strong></td>
<td></td>
</tr>
</tbody>
</table>
Existing Oral Formulations

- The ratio of amoxicillin / clavulanate has varied according to recommendations for the treatment of severe infections and of infections caused by resistant pathogens (S. Pneumoniae)
  - 2/1 is no longer recommended
  - 4:1 is the most commonly available option
  - 7-8:1 would be the best compromise
  - 14-16:1 is unaffordable
4:1 ratio

• Dosages
  – Suspension 125 mg amoxicillin / 31.25 mg
  – Tabs 500 mg amoxicillin / 125 mg

• Indications: 50 mg/kg/d (3 doses) but no longer recommended for pediatric use in 2016

• Included in the WHO PEDL and most of the MoH lists

• Due to side effects of clavulanate, there is need to increase the amoxicillin component
Duo 7-8:1 ratio

- **Dosages**
  - Suspension 400 or 500 mg amoxicillin / 57 or 62.5 mg
  - Tabs 500 or 875 mg amoxicillin / 62.5 or 125 mg
- **Indications:** 50-80 mg/kg/d (2 doses) for severe pneumonia, AOM and severe soft tissues infections
- **Not included in the WHO PEDL or in MoH lists**
- **At 50 mg/kg/d cannot cover resistant S. Pneumoniae, specifically in immuno-compromised children**
- **Problems at 80 mg/kg/d due to the side effects of clavulanate (diarrhea, liver and renal toxicity especially in vulnerable children)**
14-16:1 ratio

- **Dosages**
  - 14:1 Suspension 600 mg amoxicillin / 42.9 mg (pediatric)
  - 16:1 Tabs 2000 mg amoxicillin / 125 mg (> 40 kg)

- **Indications:** 90 mg/kg/d (2 doses) for severe pneumonia, AOM and severe soft tissues infections

- **Not included in the WHO PEDL or in MoH lists and not accessible with current price and formulation**

- **Ideal and absolutely necessary in immuno-compromised children to reach the desired dosage of amoxicillin without side effects of clavulanate**
Clavulanate instability

- Whatever the ratio, clavulanate is unstable in field conditions

- The loss of activity was estimated by the manufacturer (Sandoz) at 13% over 7 days at 2-8°C, leading to a lower dosage of clavulanate over time

- Consequences of this under dosage on the emergence of resistant strains
Alternative Solution: CEFUROXIME

- Question on the resistance of this C2G
- 30mg/kg/d divided in 2 doses
- Oral suspension 125 mL/5mL and tabs 250 mg
- Expensive
- Not in the WHO Pediatrics Essential Drugs List revised in April 2015 and not in MoH lists
Conclusion

• Potential clavulanate toxicity (digestive tract, liver and kidney)
• Instability of clavulanate in suspension
• No access to the ideal ratio

- Need for a stable and affordable dispersible tablet of co-amoxiclav with a 14:1 ratio, included in the WHO PEDL and MoH lists
- Consistently High Bacteriological Success Rates
Two potential other projects

**Cloxacillin**
- Suspected low bioavailability (MIC remains low)
- Need for a better and affordable Penicillin M

**Clindamycin**
- Benzyl alcohol not metabolized by neo-nates (risk of respiratory distress and lethal apnea)
- Need for alcohol free drug
THANK YOU FOR YOUR ATTENTION

References
