Penicillin as an essential medicine for rheumatic heart disease primary and secondary prevention

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Outline

1. Pathogenesis of RHD
2. Burden of RHD (in SA)
3. Effect of penicillin on ARF
4. Public health importance of penicillin
5. Problems with supply, quality and complications
6. What can be done: Zambia programme
7. Actions
Pathogenesis of Rheumatic Heart Disease

S. pyogenes → Infection → Immune response → First episode of ARF → RHD

- Appropriate immune response
- Inappropriate autoimmune response

Recurrent ARF
<table>
<thead>
<tr>
<th>Region</th>
<th>2000</th>
<th>2012</th>
<th>% change</th>
<th>2000</th>
<th>2012</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>371,937</td>
<td>337,335</td>
<td>−9%</td>
<td>14,312,769</td>
<td>11,953,850</td>
<td>−16%</td>
</tr>
<tr>
<td>HIC</td>
<td>37,740</td>
<td>29,690</td>
<td>−21%</td>
<td>1,191,486</td>
<td>858,392</td>
<td>−28%</td>
</tr>
<tr>
<td>AFR*</td>
<td>32,438</td>
<td>32,968</td>
<td>2%</td>
<td>1,662,132</td>
<td>1,643,539</td>
<td>−1%</td>
</tr>
<tr>
<td>AMR</td>
<td>11,627</td>
<td>11,087</td>
<td>−5%</td>
<td>425,373</td>
<td>357,439</td>
<td>−16%</td>
</tr>
<tr>
<td>SEAR</td>
<td>147,746</td>
<td>131,220</td>
<td>−11%</td>
<td>5,863,333</td>
<td>4,869,508</td>
<td>−17%</td>
</tr>
<tr>
<td>EUR</td>
<td>25,989</td>
<td>21,824</td>
<td>−16%</td>
<td>945,094</td>
<td>691,360</td>
<td>−27%</td>
</tr>
<tr>
<td>EMR*</td>
<td>34,523</td>
<td>35,305</td>
<td>2%</td>
<td>1,263,994</td>
<td>1,238,496</td>
<td>−2%</td>
</tr>
<tr>
<td>WPR</td>
<td>80,760</td>
<td>74,230</td>
<td>−8%</td>
<td>2,924,041</td>
<td>2,265,636</td>
<td>−23%</td>
</tr>
</tbody>
</table>

AFR, African region; AMR, American region; EMR, Eastern Mediterranean region; EUR, European region; DALYS, disability adjusted life years; HIC, high-income countries; RHD, rheumatic heart disease; SEAR, Southeastern Asia region; WPR Western Pacific region.

*Note that in AFR and EMR there has been little change.

Yusuf, Narula and Gamra. Global Heart 2017
Figure. Decline of the incidence of rheumatic fever with the introduction of a comprehensive program that included treatment of all clinically suspected streptococcal sore throats.

Ganesan Karthikeyan, and Bongani M. Mayosi Circulation. 2009;120:709-713
Figure 1. NZ first episode ARF hospitalisation rates per 100,000 population per year

Baseline 2009/11 4.0 per 100,000

BPS Target 2017 1.4 per 100,000

RFPP began implementation

NB. This graph deliberately uses crude rates to be consistent with method used for specifying the ARF Better Public Services baseline and target rates (see Table 4 for age-standardised rates later in the report)
Fig. 5. Rheumatic heart disease mortality rate, 1997–2012.

Liesl J. Zühlke, Mark E. Engel, David Watkins, Bongani M. Mayosi

Incidence, prevalence and outcome of rheumatic heart disease in South Africa: A systematic review of contemporary studies

How To Eliminate ARF and Reduce Mortality and Morbidity from RHD?

- Economic development with greater government investment in housing and health;
- Reduction of poverty;
- Improved penicillin prophylaxis for both primary and secondary prevention, and prompt treatment of sore throat;
- Appropriate medical (e.g., heart failure, atrial fibrillation) and interventional therapies (e.g., mitral valve balloon angioplasty and surgery)
Effectiveness of Penicillin
Primary Prevention: Large Effect

Comparison: 02 Penicillin versus control
Outcome: 01 Incidence of Rheumatic Fever

<table>
<thead>
<tr>
<th>Study</th>
<th>Penicillin n/N</th>
<th>Control n/N</th>
<th>RR (95% CI Fixed)</th>
<th>Weight %</th>
<th>RR (95% CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennke, 1951</td>
<td>0 / 174</td>
<td>0 / 164</td>
<td>0.0</td>
<td>Not Estimable</td>
<td></td>
</tr>
<tr>
<td>Brink, 1951</td>
<td>2 / 157</td>
<td>5 / 158</td>
<td>7.6</td>
<td>0.04(0.08,2.05)</td>
<td></td>
</tr>
<tr>
<td>Broock, 1963</td>
<td>0 / 262</td>
<td>1 / 87</td>
<td>3.4</td>
<td>0.11(0.06,2.71)</td>
<td></td>
</tr>
<tr>
<td>Brummitt, 1957</td>
<td>0 / 62</td>
<td>0 / 53</td>
<td>0.0</td>
<td>Not Estimable</td>
<td></td>
</tr>
<tr>
<td>Chamovitz, 1954</td>
<td>0 / 162</td>
<td>2 / 109</td>
<td>4.2</td>
<td>0.17(0.01,3.41)</td>
<td></td>
</tr>
<tr>
<td>Denny, 1955</td>
<td>2 / 798</td>
<td>17 / 834</td>
<td>25.0</td>
<td>0.12(0.03,0.51)</td>
<td></td>
</tr>
<tr>
<td>Denny, 1953</td>
<td>1 / 53</td>
<td>1 / 53</td>
<td>1.6</td>
<td>0.94(0.06,14.60)</td>
<td></td>
</tr>
<tr>
<td>Siegel, 1961</td>
<td>0 / 506</td>
<td>2 / 665</td>
<td>3.6</td>
<td>0.20(0.01,14.14)</td>
<td></td>
</tr>
<tr>
<td>Wannamaker, 1951</td>
<td>7 / 1178</td>
<td>35 / 1162</td>
<td>53.7</td>
<td>0.20(0.08,0.44)</td>
<td></td>
</tr>
</tbody>
</table>

Total(95% CI): 12 / 3464 63 / 3238
Test for heterogeneity chi square=2.57 df=6 p=0.6
Test for overall effect z=-5.39 p<0.00001

Robertson, Volmink and Mayosi. BMC Cardiovascular Dis 2005
Penicillin for secondary prevention of rheumatic fever

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Penicillin n/N</th>
<th>Placebo / Control n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kohn 1953</td>
<td>3/40</td>
<td>19/106</td>
<td></td>
<td>0.42 [0.13, 1.34]</td>
</tr>
<tr>
<td>Feinstein 1966</td>
<td>1/82</td>
<td>2/79</td>
<td></td>
<td>0.48 [0.04, 5.21]</td>
</tr>
<tr>
<td>Padmavati 1973</td>
<td>11/523</td>
<td>22/471</td>
<td></td>
<td>0.45 [0.22, 0.92]</td>
</tr>
</tbody>
</table>
Penicillin for secondary prevention of rheumatic fever

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Intramuscular n/N</th>
<th>Oral n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feinstein 1959</td>
<td>1/116</td>
<td>15/113</td>
<td>0.06 [0.01, 0.48]</td>
</tr>
<tr>
<td>Wood 1964</td>
<td>2/146</td>
<td>30/143</td>
<td>0.07 [0.02, 0.27]</td>
</tr>
<tr>
<td>Feinstein 1965</td>
<td>1/136</td>
<td>18/101</td>
<td>0.04 [0.01, 0.30]</td>
</tr>
<tr>
<td>Feinstein 1968</td>
<td>3/163</td>
<td>26/180</td>
<td>0.13 [0.04, 0.41]</td>
</tr>
</tbody>
</table>

Cochrane Database of Systematic Reviews
22 JUL 2002 DOI: 10.1002/14651858.CD002227
Penicillin as a WHO Essential Drug

- Treatment of syphilis and other treponemal diseases (e.g., yaws)
- Primary and secondary prevention of ARF
- Prophylaxis against respiratory infections in sickle cell disease
- Prophylaxis against recurrent meningococcal meningitis
- Post-splenectomy patients
- Intrapartum prophylaxis of group B streptococcal disease
Barriers to the use of penicillin
These same drivers were reported as barriers across countries surveyed.

Clinician reported barriers to BPG use, by country (n=14)

Adverse outcomes and pain are linked to perceived quality issues by clinicians.

Barriers may lead clinicians to substitute BPG with oral penicillins, which impacts overall demand for BPG.

Source: Survey of clinicians in 14 CHAI countries.
Proportion of availability of injectable penicillin in all facilities (AFRO)
Rheumatic Heart Disease Program
Zambia
BeatRHD Zambia

Program summary

• Goal: eliminate RHD in Zambia in our lifetime through research, health system strengthening, and public awareness.

• Joint effort of multiple partners including Lusaka University Teaching Hospital, MOH, University of Zambia, Zambia Paediatric Association, and Pan-African Society of Cardiology (PASCAR).

• BeatRHD Zambia is led by Dr. John Musuku at University Teaching Hospital
BeatRHD Zambia

Training for nurses and doctors

- BeatRHD Zambia helps nurses and doctors across Zambia learn how to prevent RHD and how to give good care to patients with RHD.

- The training is conducted with flipcharts, videos, and tablets.

RHD awareness and training videos utilised
Fear of adverse reactions to BPG was one of the greatest barriers to routine administration.
INTERVENTIONS

Classroom teaching
Interactive workshops
Hands-on demonstrations
Durable educational materials
Video and flipcharts
Key elements of the Zambian Programme

- Training: Creation of durable and accessible educational materials
- Allergy: Compilation and provision of penicillin allergy kits
- Drug supply: Provision of 25,000 vials of BPG by Sandoz
- Mentorship: Ongoing supportive supervision in clinics
Outcomes

• Baseline information obtained from the initial workshop indicated an extremely low (and perhaps even zero) rate of usage of BPG for primary and secondary prevention of RHD among health workers at UTH and Lusaka area government health facilities.

• Two years later, there were substantial changes in the pattern of BPG usage as result of the program’s interventions. 21 government health facilities in Lusaka were enrolled into the RHD control program and records indicate that more than 9,000 doses of BPG had been administered as a result of the program, the majority of which was used for primary prevention of RHD.

• No case of anaphylaxis had been recorded.

• Further scale-up of the RHD control program in Lusaka Province is underway, as is expansion to Southern Province. Extension to additional provinces is anticipated in 2017.
In certain areas of the world there is even greater fear.

Describes areas of heightened concern in parts of India (Nepal, Tamil Nadu and Kerala).
In Nepal, there are reports that health workers have been assaulted or jailed following adverse reactions to BPG.\textsuperscript{181} In Brazil, nursing staff have been so concerned about the risks of administering BPG in primary care the nursing council limited the practice.\textsuperscript{120} There are unconfirmed reports that BPG has been banned in some states in India (Kerala and Tamil Nadu) because of fear of ADRs.\textsuperscript{182,183} In Zambia, fear of anaphylaxis prevented health care workers adhering to standard treatment guidelines.\textsuperscript{184}
Issues

• BPG shortages
  • Affected countries: incl Australia, India and S Africa

• Challenges for the supply and use of BPG
  • Limited no. of manufacturers of APIs
  • Poor visibility of demand
  • Aggressive price reduction policies in procurement
  • Fragmented and low volume markets
  • Business decisions by manufacturers
Issues II

• Challenges for the supply and use of BPG
  • Adverse drug reactions to BPG
  • Quality and behaviour of BPG
  • Antibiotic resistance

• Opportunities to improve BPG
  • Options for product reformulation (paeds, pain, longer acting)
  • Regulatory issues (historic licensing data; extending licensing to novel indications)
Actions and Recommendations

• Global: convene stakeholders in global BPG market to develop a joint strategy to revive and redevelop BPG.
• Regional: develop regional partnership with support of WHO regional offices
• National: 13 actions
• Local: guidelines, training, adrenaline and patients
National Actions

• 1. Ensure BPG recommendations are in the national EMLs and Formularies;
• 2. Engage with WHO-led efforts to develop a systematic approach to prevent and manage shortages of essential medicines;
• 3. Include procurement of BPG in national budgets in line with the WHO Package of Essential NCD interventions (PEN) Packages;
• 4. Create an emergency national plan for cases of unpredictable shortages and stock outs where BPG is unavailable;
• 5. Develop support mechanisms for clinicians and communities to notify drug shortages or to be alerted to expected shortages.
In conclusion

• Ensure all required medications are registered with national regulator and included on national formulary/essential medicines list;
• Train programme staff on effective forecasting, quantification, procurement and distribution;
• Strengthen information systems used to manage procurement and distribution of medicines;
• Consider mHealth solutions to reduce risk of stock outs;
• Advocate for BPG production solutions at a global level