Multidrug resistant tuberculosis. Where next?

Professor Peter D O Davies
(Liverpool)
DOTS + and LTBI
New drugs for TB and the challenge of resistance – talk plan

1. Epidemiology

2. Treatment

3. The MDRTB service

4. New drugs and drug trials
Definitions

- Multidrug-resistant tuberculosis (MDRTB)
- Resistance to Isoniazid and Rifampicin

- Extensively (extremely) drug-resistant (XDR-TB)
- MDR-TB plus resistance to a second line injectable drug such as amykacin plus a quinolone.
Figure 1.1. Tuberculosis case reports and rates, UK, 2000-2009
Drug resistance in the UK

![Figure 2.1. Proportion of tuberculosis cases with first-line drug resistance, UK, 2000-2009](image)
Primary MDR TB in U.S.-born vs. Foreign-born Persons, United States, 1993–2008*

*Updated as of May 20, 2009.

Note: Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.

• 424,000 (95% CI 376,000-620,000) 2.9% of all cases.

• 181,000 (95% CI 135,000-319,000) 15.3% previously treated.

• China, India, Russian Fed: 62% of global burden.

* Sub-national coverage in India, China, Russia, Indonesia.

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2006. All rights reserved.

* Sub-national coverage in India, China, Russia, Indonesia.

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

© WHO 2006. All rights reserved.
Countries with XDR-TB confirmed cases as of June 2008

Based on information provided to WHO Stop TB Department - June 2008
New drugs for TB and the challenge of resistance – talk plan

1. Epidemiology

2. Treatment

3. The MDRTB service

4. New drugs and drug trials
Currently recommended treatment of fully sensitive tuberculosis

- Isoniazid
- Rifampicin
- Pyrazinamide
- Ethambutol/Streptomycin
- For 2 months or until sensitivities available
- Then
- Isoniazid and Rifampicin for 4 months
- 10 months for CNS TB
- Use FDCs where possible
Drug resistance - risk factors

- A. Previous treatment especially if prolonged
- B. Contact with drug resistant patient
- C. Country of origin
  - East Europe
  - Former USSR
  - Middle East
  - South and SE Asia
  - Latin America
  - Africa
- D. Age (In MDR area, commoner in children)
- E. HIV (Where MDR common)
- F. Substance abuse and homelessness
Table of drugs used for the treatment of tuberculosis.

<table>
<thead>
<tr>
<th>First line drugs</th>
<th>Second line drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Essential</strong></td>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>Gp1 Isoniazid</td>
<td>Gp1 Pyrazinamide</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Ethambutol</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>New</strong></td>
<td></td>
</tr>
<tr>
<td>Rifamycins</td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td></td>
</tr>
<tr>
<td>Rifapentine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Possible regimens according to patterns of drug resistance (1)**

<table>
<thead>
<tr>
<th>Resistance to…</th>
<th>Suggested regimen:</th>
<th>Length</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid and PZI</td>
<td>RIF, E, Mox, (Pro, Cyclo Amik)</td>
<td>9 months to a year</td>
<td>Anticipate good response</td>
</tr>
<tr>
<td>Isoniazid and E</td>
<td>RIF, PZI, Mox, (Pro, Cyclo Amik)</td>
<td>9-12/12</td>
<td></td>
</tr>
<tr>
<td>Isoniazid and RIF</td>
<td>Amik, PZI, E, Mox, Pro, Cyclo</td>
<td>At least 18/12</td>
<td>Consider surgery</td>
</tr>
</tbody>
</table>
Possible regimens according to patterns of drug resistance (2)

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Suggested regimen</th>
<th>Length</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH, RIF, Amik, moxi</td>
<td>Z, E, Pro, Cyclo, PAS, Clo</td>
<td>18-24/12</td>
<td>Consider surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After cul-ve</td>
<td></td>
</tr>
<tr>
<td>INH, RIF, Z, E, Amik, Moxi,</td>
<td>Pro, Cyclo, PAS, Clo, Am/Clav, Li</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>Assume</td>
<td>Resistance</td>
<td>To Strep</td>
<td>Unless Sensitivity</td>
</tr>
</tbody>
</table>


New drugs for TB and the challenge of resistance – talk plan

1. Epidemiology

2. Treatment

3. The MDRTB service

4. New drugs and drug trials
National MDR-TB Service

- **Need as MDRTB so uncommon**

- Agreement of relevant professional bodies
- e virtual committee of experts
- Give advice re: management
- Patient data and progress
- Follow up advice and management
- Voluntary
- Outcomes: bacteriological and clinical.

**MDRTBservice@lhch.nhs.uk**
Proposal for the management of drug resistant tuberculosis

- All MDRTB specimens identified by reference lab.
- Clinician managing patient informed by lab director
- Clinician informed about MDRTB service
- Clinician invited to contact MDRTBS re management
- Asked to complete data entry form by MDRTBS
- Details entered onto blog by MDRTBS
- E committee informed of new case on Secure Blog.
- Advice entered onto blog and emailed to managing clinician
- Three-monthly clinical updates from clinician to coordinator.

Regular meetings convened by lead clinician
Composition of virtual e-committee

• Microbiologists/Lab directors  5
• Chest Physicians            13
• ID Physicians               5
• HIV physicians              1
• Paediatricians              5
• Public Health Physicians    3
• Respiratory Pharmacist      1
• TB Specialist nurse         1
• Surgeon                     1
• Total                       35
• Patient                     (1)
E mail message

• A reminder of how to log on to the new MDRTB secure web based discussion forum.
• (URL and log on details below, upper case essential):-

  •
  • [http://mdrtbservice.typepad.com/](http://mdrtbservice.typepad.com/)
MDRTB SERVICE

MDRTB 70

29 year old housewife, married with 2 children aged 3 and 5.


As child aged about 6 had what sounds like chemoprophylaxis following positive mantoux (was not unwell at time). Otherwise no previous TB. No known TB contact.

6 week history of cough, and few days haemoptysis. CXR infiltrates and probable cavity RUL.

Sputum smear positive. Cultures awaited but in view of country of origin molecular testing for drug resistance done. This suggests resistant to both Rifampicin and Isoniazid.

Weight 54kg.

I have admitted to negative pressure room. Plan to start 6 drugs:

- Amikacin 15mg/kg iv
- Moxifloxacin 400mg
- Ethambutol 800mg
- Pyrazinamide 2g
- Prothionamide build up dose to 500mg bd if tolerated
- Cycloserine build up dose to 500mg bd if tolerated

Vitamin D status awaited. HIV no known risk factors - plan to discuss getting test in next few days.

Contact screening for family to be arranged shortly - I note current consensus (which I agree with) is not to give chemoprophylaxis if they turn out to have LTBI.

Will update further when more information available.

Jul 17 2010
Looks like you have covered all the bases. What about extent of disease with a view to surgery?

Posted by: Peter Davies | December 17, 2009 at 09:14 AM

I would have sent the transbronchial biopsy for culture as well. In the face of TB within the family, sarcoid seems less likely. However, I would not have been keen to treat until a positive mycobacterial culture had been obtained.

As yet chemoprophylaxis for drug-resistant TB is not recommended. The literature on the value of IGRA in children suggests the immunostop might be better.

Posted by: Graham Rothamley | March 17, 2010 at 04:57 PM

I agree with Graham and would perform T spot and probably repeat in 6 weeks time also. As if become positive would need to be more vigilant with child.

I would not treat even prophylaxis unless clear evidence of TB. Assuming not HIV +ve / immunodeficiency.

Posted by: Scott Hackett | March 18, 2010 at 09:57 AM

I agree with both Graham and Scott in that the T spot may be more useful in this setting. IF positive then would monitor for development of symptoms or radiological changes but would not put on chemoprophylaxis in the first instance. Not sure that repeat IGRA testing has been demonstrated to be useful although based on our experience with TST conversion this does make sense.

Posted by: Delano Shingadia | March 18, 2010 at 10:11 AM

I agree with comments re transbronchial biopsy and culture - crucial here. In the clinical context TB is more likely than sarcoid but would prefer positive culture before...
Activity from 1/1/08 to 31/12/09

- Cases discussed = 72
  (55MDR, 4XDR 13 MDR not confirmed)

- Comments received = 300
  Most comments (15), fewest (2)

- Five most active repliers all Chest Physicians
  (75% of comments)

- ID repliers a/c for 12% of comments
Multidrug resistant tuberculosis. Where next?

1. Epidemiology

2. Treatment

3. The MDRTB service

4. New drugs and drug trials
   - Drug sensitive disease
   - Multidrug resistant disease
New drug development

Basic research  Lead discovery  Preclinical study  Clinical trials  Technology transfer

Target Identific: Selection
Assay Develop: chemistry
Pharmako- dynamics kinetics toxicology

Phase I Phase II Phase III

e.g. Proteomics animal models human volunteers RCTs

Programme evaluation safety surveillance

10 years... plus
Gati and moxi better than E and Oflox

Phase 2 study of Gati v moxi v Oflox.

Speed Culture Conversion

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2HRZE</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>2HRZG</td>
<td>[4HR]</td>
<td>1.519</td>
</tr>
<tr>
<td>2HRZM</td>
<td></td>
<td>1.683</td>
</tr>
<tr>
<td>2HRZO</td>
<td></td>
<td>0.830</td>
</tr>
</tbody>
</table>

Moxi better than H

*Phase 2 moxifloxacin*

Endpoint 2/12 culture conversion

N = 328

MRZE 60.4%

HRZE 54.9% p=0.037

AJRCCM 2009;180:273.
Ongoing Phase III Study: REMoxTB

Regimen 1
(active control)
800 patients

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>12</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-Up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Regimen 2

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>12</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-Up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Regimen 3

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>12</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-Up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comparison 1
M subst for E: (4 vs 6 mos)
Non-inferior Failure/relapse rate

Comparison 2
M subst for H (4 vs 6 mos.): Non-inferior Failure/relapse rate
Gati v Ethambutol

Gatifloxacin Phase 3

- 2HRZG/2GRH
- 2HRZE/4HR

- Endpoint cure at 24/12

- First results due June 2011.
Moxi v H and intermittent rifapentine in continuation phase

Rifaquin trial

- Recruitment 610/1110  endpoint cure at 18/12

- 2MRZE/2(RpM)_2
- 2MRZE/4(RpM)_1
- 2HRZE/4HR
- Rp 15mg/kg twice weekly
  20mg/kg once weekly
New diarylquinaline (TMC207) in MDRTB

Endpoint culture conversion at 8/52

N = 44

OBR + T  10/21 (43%)
OBR + P  2/23 (9%)  p=0.003

TMC207 in MDRTB

- TMC207 Phase 2 study
- (Oral presentation Berlin Nov:2010)

- Endpoint % culture conversion at 24/52
- HIV-ve or HIV+ve CD>300 no ART

- Eth,Z,Ofl,Kan,Cyclo + P 58%
  + T 79%  p=0.008

- Time to 50% conversion 12 v 18/52 0.003
Bangladesh MDRTB regimen plus Clofaz (STREAM study)

Recruitment 600
Endpoint Culture –ve 27/12

2 4KHMEZC/5MEZC Clofazimine
1 Standard GLC
Further Phase 1 and 2 studies

- Nitroimidazole        PA-824
- Oxazolidinone        (Linezolid)
- Ethylenediamine      SQ 109
- High dose rifamycins
“If you give two vaccines where the only thing in common is the antigen, it seems to focus and enhance the immune response.”

Modified vaccinia virus + antigen 85A

A prime boost
A new vaccine for tuberculosis

In Oxford and beyond, trials have begun on a new vaccine for tuberculosis – the first since BCG was developed 80 years ago.
Summary

• No new drugs for TB for 40 years.
• Urgent need because of length of treatment for DSD and increasing MDRTB
• Newer Fluoroquinolones effective in early trials.
• Now being developed in regimen shortening trials for drug sensitive disease.
• Diarylquinoline TMC207 in Phase 2 study seems very promising in MDRTB.
• Other drugs including high dose rifamycins in pipeline.
Wallace Fox
1920 - 2010
Activity from 1/1/08 to 31/12/09

- Cases discussed 72
  - (55 MDR, 4 XDR, 13 MDR not confirmed)

- Comments received 300
- Most comments (15), fewest (2)

- Five most active repliers all Chest Physicians (75% of comments)

- ID repliers a/c for 12% of comments
# New drug development

<table>
<thead>
<tr>
<th>Basic research</th>
<th>Lead discovery</th>
<th>Preclinical study</th>
<th>Clinical trials</th>
<th>Technology transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td><strong>Assay</strong></td>
<td><strong>Pharmako-</strong></td>
<td><strong>Phase I</strong></td>
<td><strong>Phase IV</strong></td>
</tr>
<tr>
<td><strong>Identific:</strong></td>
<td><strong>Develop:</strong></td>
<td><strong>dynamics</strong></td>
<td><strong>Phase II</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Selection</strong></td>
<td><strong>chemistry</strong></td>
<td><strong>kinetics</strong></td>
<td><strong>Phase III</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Proteomics</strong></td>
<td></td>
<td><strong>toxicology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>•</td>
<td></td>
<td><strong>animal models</strong></td>
<td><strong>human volunteers</strong></td>
<td><strong>Programme evaluation</strong></td>
</tr>
<tr>
<td>•</td>
<td></td>
<td></td>
<td><strong>RTCs</strong></td>
<td><strong>safety surveillance</strong></td>
</tr>
</tbody>
</table>
Mouse trials with moxifloxacin

2HRZ/4HR
1MRZ/4MR
2MRZ/3MR
5MRZ

No bacterial growth at month 4.
2HRZ/4HR relapsed at 4 and 5 months.

Phase 2 study of Gati v moxi v Oflox.

IJTLD 2008;12:128

- Endpoint Sputum colony counts

  speed conversion

- 2HRZE 1
- 2HRZG [4HR] 1.519
- 2HRZM 1.683
- 2HRZO 0.830
Phase 2 moxifloxacin
AJRCCM 2009;180:273

- Endpoint 2/12 culture conversion

- 328
- MRZE 60.4%
- HRZE 54.9%  p=0.037
Ongoing Phase III Study: REMoxTB

Regimen 1 (active control)
800 patients
- EHRZ + M placebo
- HR + M placebo
- HR

Regimen 2
800 patients
- MHRZ + E placebo
- HR + M placebo
- HR

Regimen 3
800 patients
- EMRZ + H placebo
- MR+ H placebo
- HR placebo

Comparison 1
M subst for E:
(4 vs 6 mos)
Non-inferior Failure/relapse rate

Comparison 2
M subst for H
(4 vs 6 mos.):
Non-inferior Failure/relapse rate

Visits

Months
0  2  4  6  12  18

Screening  Intensive  Continuation  Follow-Up
Treatment Phase
Gatifloxacin Phase 3

- 2HRZG/2GRH
- 2HRZE/4HR
- Endpoint cure at 24/12
- First results June 2011.
TMC207 in MDRTB

• Endpoint culture conversion at 8/52

• 44

• OBR + T 10/21 (43%)

• OBR + P 2/23 (9%)  p=0.003
TMC207 Phase 2

- Endpoint % culture conversion at 24/52
- HIV-ve or HIV+ve CD>300 no ART

- Eth,Z,Ofl,Kan,Cyclo + P  58%
- + T   79%   p=0.008

- Time to 50% conversion 12 v 18/52  0.003
Rifaquin trial

• The effect of high dose rifapentine + Moxi
• Recruitment 610/1110  endpoint cure at 18/12

• 2MRZE/2(RpM)₂
• 2MRZE/4(RpM)₁
• 2HRZE/4HR
• Rp 15mg/kg twice weekly
• 20mg/kg once weekly
STREAM study

Recruitment 600
Endpoint Culture –ve 27/12

2 4KHMEZC/5MEZC Clofazimine
1 Standard GLC
Further Phase 1 and 2 studies

- Nitroimidazole        PA-824
- Oxazolidinone        (Linezolid)
- Oxazolidinone        PNU 100480
- Ethylenediamine      SQ 109
- High dose rifamycins

- [http://www.ctu.mrc.ac.uk/research_areas/tuberculosis.aspx](http://www.ctu.mrc.ac.uk/research_areas/tuberculosis.aspx)
- [http://www.theunion.org/](http://www.theunion.org/)
Summary

• No new drugs for TB for 40 years.
• Urgent need because of length of treatment for DSD and increasing MDRTB
• Newer Fluoroquinolones effective in early trials.
• Now being developed in regimen shortening trials for drug sensitive disease.
• Diarylequinoline TMC207 in Phase 2 study seems very promising in MDRTB.
• Other drugs including high dose rifamycins in pipeline.
Warning

• A new plague is sweeping across the planet

• Soon multidrug resistant tuberculosis will kill one person in three

• The Constant Gardener November 2005
First line drug resistance in the UK
<table>
<thead>
<tr>
<th>First line drugs</th>
<th>Second line drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential</td>
<td>Other</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>(Gp 1)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Ethambutol</td>
</tr>
<tr>
<td>(Gp 1)</td>
<td>(Gp 2)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Streptomycin</td>
</tr>
<tr>
<td>(Gp 1)</td>
<td>Capreomycin</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Amikacin</td>
</tr>
<tr>
<td>(Gp 2)</td>
<td>Kanamycin</td>
</tr>
<tr>
<td>(Gp 4)</td>
<td>Ethionamide</td>
</tr>
<tr>
<td>(Gp 4)</td>
<td>Cycloserine</td>
</tr>
<tr>
<td>(Gp 4)</td>
<td>PAS</td>
</tr>
<tr>
<td>(Gp 4)</td>
<td>Thioacetazone</td>
</tr>
<tr>
<td>Quinolones (Gp 3)</td>
<td>ofloxacin</td>
</tr>
<tr>
<td></td>
<td>levofloxacin</td>
</tr>
<tr>
<td></td>
<td>moxifloxacin</td>
</tr>
<tr>
<td>Quinolones (Gp 3)</td>
<td>Macrolides (Gp 5)</td>
</tr>
<tr>
<td></td>
<td>clarithromycin</td>
</tr>
<tr>
<td>New rifamycins</td>
<td>Clofazimine</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Amoxycillin &amp;</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>Clavulanic acid</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
</tr>
</tbody>
</table>
## Possible regimens according to patterns of drug resistance

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Suggested regimen</th>
<th>Length</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid and PZI</td>
<td>Amik, RIF, E, Mox</td>
<td>9 months to a year</td>
<td>Anticipate good response</td>
</tr>
<tr>
<td>Isoniazid and E</td>
<td>Amik, RIF, PZI, Mox.</td>
<td>9-12/12</td>
<td></td>
</tr>
<tr>
<td>Isoniazid and RIF</td>
<td>Amik, PZI, E, Mox.</td>
<td>At least 18/12</td>
<td>Consider surgery</td>
</tr>
</tbody>
</table>
Possible regimens according to patterns of drug resistance

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Suggested regimen</th>
<th>Length</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH, RIF, PZI</td>
<td>Amik, E, Mox, Eth, Cy</td>
<td>18-24/12</td>
<td>Consider surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After cul-ve</td>
<td></td>
</tr>
<tr>
<td>INH, RIF, PZI, E</td>
<td>Amik, Mox. Eth, Cy, Clar</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>Assume</td>
<td>Resistance</td>
<td>To Strep</td>
<td>Unless Sensitivity</td>
</tr>
</tbody>
</table>