4th Global Laboratory Initiative Partners' Meeting,
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"Totally Drug-Resistant" Tuberculosis: A WHO consultation on the diagnostic definition and treatment options

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Events in India

- Letter by Z Udwadia et al published on line on 21 December 2011 in Clinical Infectious Diseases (DOI: 10.1093/cid/cir889), subsequently as CID (2012) 54(4):579-581
- 4 patients, Hinduja Hospital, Mumbai
- Resistant to all 12 drugs tested
- Erratic treatment in private sector held responsible

Media Response

7th January, major media pick it up, link it with previous reports in Iran and Italy.
WHO implicated as having certified the hospital lab.
8 more patients reported.

New, deadlier form of TB hits India

Malathy Iyer, TNN Jan 7, 2012, 05.39AM IST

Tags: World Health Organization | Tuberculosis | TB

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MUMBAI: Tuberculosis, which kills around 1,000 people a day in India, has acquired a deadlier edge. A new entity-ominously called Totally Drug-Resistant TB (TDR-TB)-has been isolated in the fluid samples of 12 TB patients in the past three months alone at Hinduja Hospital at Mahim . The hospital's laboratory has been certified by the World Health Organization (WHO) to test TB patients for drug resistance.

While Iran first reported TDRTB cases three years ago, India seems to be only the second country to report this deadly form of the disease. TDR-TB is the result of the latest mutation of the bacilli after Multi-Drug-Resistant TB (MDR-TB) and Extremely Drug-Resistant TB (XDR-TB) were diagnozed earlier.

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Issues Raised

- Is "totally drug resistant" TB an appropriate definition?
  - Poor reliability of DST for second-line bacteriostatic drugs
  - Common sense definition vs global or national agency definition
  - Is it really "XDR"? Or "XXDR"?
- Isolation
- Causation
- Treatability
- Availability of Group 5 drugs
- Transmissibility

WHO decided to organise consultation

Participants

- Technical agencies (CDC, KEMRI, KNCV, Union, USAID)
- Lab experts (SRL)
- Clinical experts (Hinduja, MSF, PiH)
- Epidemiological experts (McGill)
- Civil Society (MSF, PiH,TAG,)
- National TB Programmes (Brazil, India could not attend)
- Pharmaceutical companies (GATB, Tibotec–Janssen, Otsuka)
- gGLC
- MDR-TB Working Group
- WHO staff (HQ, ROs, COs)

Questions

- Is a new definition, beyond XDR-TB, appropriate?
  - Criteria proposed by gGLC:
  - Outcomes should be significantly different
  - Laboratory methods must be reliable
  - Both clinical and surveillance needs should be addressed
- What treatment options are available?

New Definitions Discussions

- Technical difficulties with DST of several anti-TB medicines
- Only resistance to drugs defining XDR-TB (isoniazid, rifampicin, injectables and fluoroquinolones (FQ)) adequately reliable
- DST for Group 4 drugs un-reproducible
- Lack of standardised DST methods for several anti-TB drugs (including new investigational drugs and Group 5 drugs)
- Molecular DST offers promise: however,
  - few mutations conferring resistance described for most second-line drugs
  - testing technically demanding and expensive.
  - Molecular DST for SLDs cannot yet replace phenotypic
- Civil society and advocates against new definition
- Insufficient evidence to link such DST results to treatment outcomes of patients

Outcomes of XDR-TB+ in IPD

- Individual Patient Database ("IPD") of MDR-TB cases
- 8955 MDR-TB cases from 32 sites
- 6724 cases had DST results for at least one fluoroquinolone and one 2nd line injectable
- 405 XDR-TB cases
  - (i) resistant to all 2nd line injectables (N=82)
  - (ii) resistant to all 2nd line injectables plus any other drug tested (N=32)
  - (iii) resistant to all drugs tested which included at least one Group 4 drug (N=48).

Outcomes of XDR-TB+ in IPD - I

- Deaths increased from 18% to 27% to 30% in groups (i), (ii) and (iii) respectively – thus higher than XDR-TB cases with no additional resistance (14%)
- Cure in XDR-TB and no additional resistance was 44%, in XDR-TB with additional resistance 24-34%
- However, after adjustment, **no significant differences** were observed in the outcomes of these different XDR-TB groups.
- CDC's Preserving Effective TB Treatment Study (PETTS) showed same for outcomes with resistance to all 3 injectables vs resistance to only one or two

Conclusions

- Increasing reports severe patterns of drug resistance, worse than XDR-TB
- A new definition of resistance beyond XDR-TB not recommended
- Further work on existing databases to review impact of XDR + resistance to all injectables, and XDR + resistance to later generation FQs, and both
- All injectables and all fluoroquinolones should be tested routinely in specimens from confirmed MDR-TB patients
- Pharmaceutical companies to collaborate early to use new drugs in novel combination regimens
- Collaboration between national TB control programmes, Ministries of Health, drug regulatory agencies and pharmaceutical companies to facilitate compassionate use of new TB drugs
- Properly conducted studies needed, in different epidemiological settings, linking DST results to patient management and clinical outcomes. Academic groups and well-organised NTPs

Actions

- CDC will examine associations between outcomes and resistance to later-generation fluoroquinolones and/or all injectable agents among XDR-TB patients in the PETTS database .
- If any findings meeting criteria for new definition, a further consultation may be in order.
- WHO Working Group* on guidance on how to improve observational studies of treatment for drug-resistant TB
- WHO/GDF to improve availability and affordability of clofazimine and linezolid
- WHO to support CPTR and other initiatives to strengthen collaboration between drug developers to come up with effective combination of drugs in the shortest possible time
- Pharmaceutical companies wishing to do compassionate use should work closely with the WHO regional offices concerned

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