Briefing Paper
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Shorter treatment for children with minimal TB

Treating children with tuberculosis

Around 1.1 million children develop tuberculosis (TB), and 205,000 children die each year from TB. Africa and South East Asia have the highest number of cases of TB in children, and children make up around 30% of TB cases in Africa.

Despite this high burden of disease among children, regimens for treating children with TB have lagged behind those for adults. Children with TB have been seen as lower priority than adults as they are rarely infectious, and it is harder to diagnose and evaluate the efficacy of treatment. Treatments for children are based on extrapolation of results from adult trials to children.

Most children with TB have non-severe and smear-negative TB (minimal TB). TB is hard to diagnose in children because they may not be able to spontaneously produce sputum, and they are more likely to have paucibacillary disease with smear-negative respiratory samples. Negative cultures are more frequent in milder forms of disease. Although never subjected to a controlled trial, it is generally agreed that non-severe TB in children needs treatment because of the risk of progression and dissemination, particularly in children <3 years and in those with HIV and/or malnutrition.

Until now, no randomised controlled trials have been carried out to look at the duration of treatment required for children with non-severe, smear-negative TB. The current recommendation that they receive six months of treatment is based on the approach used in adults. Although the implementation of standard regimens for both adults and children is attractive for programmes, the needs of

What is minimal TB?

In the SHINE trial, we defined minimal TB as TB which is both **smear negative** and **non-severe** in form. Non-severe forms of TB included in SHINE were:

- Extrathoracic lymph node TB and
- Non-severe respiratory TB (confirmed on chest x-ray):
  - » intra-thoracic lymph node TB with no significant airway obstruction and no bilateral airway narrowing
  - » uncomplicated forms of pulmonary TB (confined to one lobe with no cavities)

Key messages

- Around 1.1 million children develop TB each year, yet treatment is based on trials in adults
- Around two thirds of children with TB have non-severe disease, which may not need such a long treatment course
- Reducing the length of treatment could make treatment easier for children and caregivers, as well as reducing costs to patients and the health system
- SHINE showed that children with minimal TB do well on treatment
- SHINE found that the four month treatment was as good as the standard six month treatment for children with minimal TB
- TB programmes should consider moving from six months to four months of treatment for children with minimal TB

The SHINE trial

The SHINE trial looked at whether treatment for children with minimal TB could be shortened from six months (8 weeks HRZ(E) followed by 16 weeks HR) to four months (8 weeks HRZ(E) followed by 8 weeks HR). It was carried out in South Africa, Uganda, Zambia and India.

1204 children with minimal TB were randomised to receive either six months of treatment (as recommended in current World Health Organisation (WHO) guidelines) or four months of treatment. Children were followed-up for 72 weeks. Around one in ten children taking part were living with HIV, nearly all from Africa.

Children were treated using the new fixed-dose combination recommended by the WHO guidelines, and were dosed according to the WHO weightband dosing tables.

children with TB also need to be considered as they make up a substantial proportion of people living with TB. Costs to families and health services of implementing potentially overly long treatment regimens with added toxicity, and risks of drug-drug interactions in the HIV-infected, and problems with pill-burden and adherence are important considerations.

Administering medicines to children can be challenging, particularly if the formulation is unpalatable to the child. Even where child-friendly fixed dose combination formulations are used, with simplified dosing and dispersible tablets, caregivers may still face difficulties giving children their medicines. Social science work carried out within SHINE found that some caregivers had to adjust their daily schedule to incorporate sufficient time for giving medicine, and resort to strategies such as restraining or incentivising children. Reducing treatment length for children with minimal TB could really help.

This briefing paper looks at evidence from the SHINE trial, the first randomised controlled trial to assess the length of treatment needed for children with minimal TB.

Is four months of treatment as effective as six months treatment for children with minimal tuberculosis?

The SHINE trial showed that children with minimal TB do well on treatment. The proportion of children whose TB was successfully treated, and who were confirmed alive and well at the end of the trial was 93%. Less than 3% of children in the trial died from any cause. This should encourage national TB trials to diagnose and treat children with minimal TB.

SHINE found that the four-month regimen was as good as the standard six-month regimen for children with minimal TB. There was no difference between the six-month and four-month groups in terms of proportion of children with an unfavourable outcome (treatment failure, TB recurrence, death or on-treatment lost to follow-up) measured after children on both arms had completed 16 weeks of treatment (3% vs 3%). This was consistent across all the analyses performed, including the whole population of the trial, or just those who had confirmed TB, or just those who completely adhered to their randomised arm.

Acceptability and tolerability of the fixed dose combination

Few children had side-effects related to treatment. Levels of side-effects were similar in both arms. Out of a total of 16 adverse reactions to the study drugs of Grade 3 or higher, 11 were raised liver enzymes.

Social science work carried out within the trial found that the fixed dose combination was acceptable to caregivers. Unsurprisingly, given the challenges faced in giving children tablets, caregivers who took part in the acceptability sub-study expected to prefer the four-month regimen to the six-month regimen.

"If I talk about the movement to the hospital, four months is better, because the parents, we have our jobs, so six months are many compared to the four. Also the tablets were not so many if I compare it with the six months. When we finished the four months we were so happy!" *(Mother of a child in the four month arm of SHINE)*

Cost-effectiveness

As there was no difference in clinical outcomes between the four-month and six-month regimens, shortening treatment for children with minimal TB is likely to be cost-saving for the health system. These cost savings will be dependent on health services being able to effectively identify children with minimal TB (who can have four months treatment), and those with more severe forms who will continue to need six months of treatment. More analyses are taking place to look at this.

Identifying children with minimal tuberculosis

All children in the SHINE trial had smear tests. Children identified with TB, who were smear negative and not severely sick could go in the trial and were screened for signs of TB severity, including using a chest x-ray.

As international guidelines now recommend Gene Xpert testing rather than smear testing, the SHINE team are carrying out analysis to look at how children like those included in the SHINE trial could be identified based on Gene Xpert results and clinical data, where smear testing is not available.

Conclusions

SHINE demonstrates that it is feasible to diagnose and treat children with minimal TB in programmatic conditions.

Children with minimal TB do well on treatment, and a four-month regimen is as effective as the standard six-month regimen. This means around two thirds of children with TB could potentially be safely and effectively treated with four months of treatment rather than six months. Reducing children's treatment by two months could make treatment easier for children and caregivers, as well as reducing costs to patients and the health system.

TB programmes will need to consider issues around adding complexity to the treatment of children with TB through distinguishing children with minimal TB (who can be treated with a four-month regimen) from those who require six months of treatment.

Recommendations

Recommendations for policy and practice

- TB programmes should consider moving from six months to four months of treatment for children with minimal TB, to reduce the burden of treatment on children, caregivers and the health service
- Children with smear positive or severe forms of TB should continue to receive six months of treatment
- Policymakers should consider the impact on programmes of stratifying the length of treatment for children, with children with minimal disease receiving 4 months of treatment, and children with more severe disease receiving 6 months of treatment

Recommendations for research

- SHINE demonstrates it is possible to do high quality randomised controlled trials in children with tuberculosis – more research should be done in children with TB, to ensure they are getting appropriate treatments
- Research is needed into how to identify children with minimal disease where smear testing is not available, and to see whether it is possible to identify whether some children who could have even shorter treatment. We will do some of this work using stored samples from the SHINE trial.

Further information

These results will be presented at the annual meeting of the child and adolescent TB Working Group (16th October) and the International Union against Tuberculosis and Lung Disease Conference (24th October, abstract ref LB-2056-24). For further information email Kristen Lebeau k.lebeau@ucl.ac.uk

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