RAPID ADVICE

Treatment of tuberculosis in children

World Health Organization

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Acknowledgements

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Peter Donald (Stellenbosch University, Cape Town, South Africa), Luca Richeldi, Stefania Cerri and Simona Di Mario (University of Modena and Reggio Emilia and NHS Centre for the Evaluation of the Effectiveness of Health Care–CeVEAS, Modena, Italy), and Gregory L. Kearns and Jennifer A. Goldman (University of Missouri, Kansas City, USA) led the teams that compiled, synthesized and evaluated the evidence underlying each recommendation.

Useful feedback was provided by the External Review Group (listed on page 18).

The document was prepared by Anna Ridge, Malgorzata Grzemska, Susanne Hill (WHO) and Robert Gie (Stellenbosch University, Cape Town, South Africa).

Dorris Ortega and Madelyne Clemente (WHO) provided secretarial support.

1. Overview

1.1 Background

The World Health Organization (WHO) first published guidance for national tuberculosis control programmes on managing tuberculosis in children (hereafter called "the Guidance") in 2006. The Guidance follows the principles of a public health approach aimed at optimizing outcomes, including the quality of life and survival, of children with tuberculosis; it also serves as a reference tool for countries to adopt and adapt according to their national circumstances.

During 2009 and 2010, WHO updated the Guidance through a series of coordinated efforts to review and synthesize evidence on the correct dosages of antituberculosis medicines for use in children and the regimens that should be used for different manifestations of the disease in children. This evidence was assembled following systematic reviews, pharmacokinetic simulations and the preparation of evidence summaries, using GRADE profiles and analysis where appropriate.

There have been major developments in advancing the use of new diagnostic tools, but these tools are not recommended for the diagnosis of latent tuberculosis infection or active tuberculosis disease in children. Preventive chemotherapy for children infected with the human immunodeficiency virus (HIV) will be addressed in other guidelines published by WHO.

The availability of new evidence, specifically concerning the correct dosages of the four essential antituberculosis medicines, justified the rapid revision of WHO's Guidance.

Representatives of the Stop TB Partnership's Childhood TB sub-working group who participated in the Guidelines Group formulated this revised guideline in the format of a Rapid Advice during a meeting of the Guidelines Group held in March 2010. In addition, two experts in paediatric pharmacology contributed to the development of this Rapid Advice.

1.2 Why the need for a revision?

Since the publication of the Guidance in 2006, novel evidence has become available concerning the correct dosages of medicines for the treatment of tuberculosis in children.

The aim of this revised guideline is to establish standards for high-quality treatment of tuberculosis in children by providing evidence-based recommendations while considering the risks and benefits, acceptability, feasibility, cost and financial implications.

1.3 Guiding principles

The Guidelines Group discussed and agreed a set of principles that should be used in developing recommendations for the treatment of tuberculosis in children. The principal consideration was that the treatment of childhood tuberculosis is a public health intervention aimed at securing the greatest likelihood of survival and quality of life for the greatest numbers of children with tuberculosis. The four guiding principles are:

1. Do no harm

Introducing changes that preserve access for those children who are sickest and most in need.

2. Ensure access and equity

Ensuring that all children with tuberculosis have access to treatment with fair and equitable distribution of diagnostic and treatment services.

3. Promote quality and efficiency

Delivering the highest standards of care within a public health approach so as to achieve the greatest health impact with the optimal use of available human and financial resources.

4. Ensure sustainability

Understanding the long-term consequences of change with the vision of providing continued access to antituberculosis medicines for those in need.

In this context, the individual rights of children with tuberculosis should not be forfeited in the course of a public health approach.

2. Recommendations at a glance

- Given the risk of drug-induced hepatotoxicity, WHO recommends the following dosages of antituberculosis medicines for the treatment of tuberculosis in children:

  isoniazid (H) – 10 mg/kg (range 10–15 mg/kg); maximum dose 300 mg/day
  rifampicin (R) – 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day
  pyrazinamide (Z) – 35 mg/kg (30–40 mg/kg)
  ethambutol (E) – 20 mg/kg (15–25 mg/kg)

- Children living in settings where the prevalence of HIV is high[1] or where resistance to isoniazid is high, or both, with suspected or confirmed pulmonary tuberculosis or peripheral lymphadenitis; or children with extensive pulmonary disease living in settings of low HIV prevalence or low isoniazid resistance, should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months at the following dosages:

  isoniazid (H) – 10 mg/kg (range 10–15 mg/kg); maximum dose 300 mg/day
  rifampicin (R) – 15 mg/kg (range 10–20 mg/kg); maximum dose: 600 mg/day
  pyrazinamide (Z) – 35 mg/kg (30–40 mg/kg)
  ethambutol (E) – 20 mg/kg (15-25 mg/kg)

- Children with suspected or confirmed pulmonary tuberculosis or tuberculous peripheral lymphadenitis who live in settings with low HIV prevalence or low resistance to isoniazid and children who are HIV-negative can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug (HR) regimen for 4 months at the following dosages:

  isoniazid (H) – 10 mg/kg (range 10–15 mg/kg); maximum dose 300 mg/day
  rifampicin (R) – 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day
  pyrazinamide (Z) – 35 mg/kg (30–40 mg/kg)

- Children with suspected or confirmed pulmonary tuberculosis or tuberculous peripheral lymphadenitis living in settings with a high HIV prevalence (or with confirmed HIV infection) should not be treated with intermittent regimens (that is, twice-weekly or thrice-weekly doses).

- During the continuation phase of treatment, thrice-weekly regimens can be considered for children known to be HIV-uninfected and living in settings with well-established directly-observed therapy (DOT).

- Infants (aged 0–3 months) with suspected or confirmed pulmonary tuberculosis or tuberculous peripheral lymphadenitis should be promptly treated with the standard treatment regimens, as described above. Treatment may require dose adjustment to reconcile the affect of age and possible toxicity in young infants. The decision to

[1] Defined as countries, subnational administrative units, or selected facilities, where the HIV prevalence among adult pregnant women is ≥1% or among TB patients is ≥5%.

adjust doses should be taken by a clinician experienced in managing paediatric tuberculosis.

- Streptomycin should not be used as part of first-line treatment regimens for children with pulmonary tuberculosis or tuberculous peripheral lymphadenitis.

- Children with suspected or confirmed tuberculous meningitis should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months; the total duration of treatment being 12 months. The doses recommended for the treatment of tuberculous meningitis are the same as those described for pulmonary tuberculosis.

- Children with suspected or confirmed osteoarticular tuberculosis should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 10 months; the total duration of treatment being 12 months. The doses recommended for the treatment of osteoarticular tuberculosis are the same as those described for pulmonary tuberculosis.

- Children with proven or suspected pulmonary tuberculosis or tuberculous meningitis caused by multiple drug-resistant bacilli can be treated with a fluoroquinolone in the context of a well-functioning MDR-TB control programme and within an appropriate MDR-TB regimen. The decision to treat should be taken by a clinician experienced in managing paediatric tuberculosis.

3. Revision process

3.1 Retrieving, summarizing and presenting the evidence

A series of activities were undertaken in preparation for the meeting held in March 2010 to review the guidelines. These included:

1. Systematic reviews of the literature to establish:
    - the pharmacokinetics of rifampicin, isoniazid and pyrazinamide in children and make recommendations for dosages to be used in children;
    - the correct dosage of antituberculosis medicines in neonates and infants younger than 3 months;
    - intermittent treatment in children;
    - the chemotherapy of tuberculous meningitis in children;
    - the chemotherapy of osteoarticular tuberculosis in children;
    - the chemotherapy of tuberculous lymphadenopathy in children;
    - the use of fluoroquinolones in children.

2. Pharmacokinetic simulations of a fixed-dose formulation of ethambutol for paediatric tuberculosis and pharmacokinetic analyses of fixed-dose combinations of medicines for paediatric tuberculosis.

3. Evidence summaries and GRADE profiles (where appropriate) for the key areas addressed:
    - the comparative risk of hepatotoxicity for higher doses of isoniazid, rifampicin and pyrazinamide;
    - treatment of tuberculosis in children aged <3 months and intermittent dosing of antituberculosis medicines in children;
    - the use of streptomycin for treating uncomplicated pulmonary tuberculosis in children;
    - the evidence base for treatment regimens for tuberculous meningitis in children;
    - the evidence base for treatment regimens for osteoarticular tuberculosis in children;
    - the use of fluoroquinolones in children with multidrug-resistant tuberculosis (MDR-TB).

The systematic reviews carried out to support the recommendations contained in these guidelines resulted in the retrieval of observational studies only. The GRADE tables are not well suited to the needs of observational studies. Moreover, the summary of findings, which are a component of GRADE profiles, can only be used when providing summary estimates of effects as either relative risk, standardized mean difference or weighted mean difference; that is, when it is possible to pool data from the studies. Statistical methods for combining measures of pharmacokinetic parameters from single-arm studies are not yet validated, and methods for combining data from non-comparative observational studies are under development.

As all observational studies start as low quality in the GRADE system, additional information needed to alter the assessment of quality has to be provided by an assessment of study by study factors.

Most of the studies identified for this guideline are non-comparative observational studies, with poor reporting of outcomes as well as significant heterogeneity. The Guidelines Group therefore decided that (i) pooled estimates were not appropriate and (ii) the quality of evidence was best assessed based on the study-by-study tables that were provided to them.

The Guidelines Group was therefore presented with GRADE tables for only one question where there were comparative studies that could be presented with an overall estimate of effect (Table 2, recommendation 10).

All the study-by-study tables (summary of evidence) and the GRADE table for recommendation 10 are included in the Annex (available on the WHO web site at http://www.who.int/tb/publications/2010).

3.2 Consensus, external review and updating

The Guidelines Group meeting on the treatment of tuberculosis in children was held at WHO headquarters in Geneva, Switzerland, on 30–31 March 2010. The meeting reviewed evidence around six key areas in different sessions. Each of the sessions included presentations of the evidence, current and proposed recommendations and a risk–benefit analysis of the key questions. The proposed recommendations were reviewed and the final recommendation(s) were formulated, taking into consideration the quality of the evidence, the balance between benefits and harms, and the balance between values and preferences, cost, feasibility and other factors. If the outcomes of GRADE analysis or summary tables were inconclusive, or if it was not possible to undertake a GRADE analysis with the available data, other factors, as listed above, were taken into consideration in making a recommendation. To reach consensus, the group took into account the factors listed above and reviewed the risk–benefit tables to make decisions on recommendations.

In the case of Recommendation 5 (on intermittent administration of medicines in the continuation phase of treatment), there was no initial consensus. Therefore, further discussion took place by e-mail and conference call resulting in a final decision.

The key recommendations were summarized in “recommendation tables” according to the six key areas, and included a summary of key factors that were considered in making the recommendations.

The summary recommendations were sent for peer review to independent reviewers, who were members of the Childhood TB sub-working group of the Stop TB Partnership, and six WHO regional TB advisers. The peer reviewers also received the risk–benefit tables, which included the strength of the evidence and the strength of the recommendation; they were asked to provide feedback on whether they agreed with the recommendations, and if not why not; and whether there were any key points that were not addressed that should be included. Feedback was received in writing from members of the External Review Group (listed on page 18).

Overall, there was strong support for the proposed recommendations from different countries and perspectives. Comments received from peer review were shared with the Guidelines Group by e-mail. The draft recommendations and recommendation tables were reviewed again, and finalized.

Based on all of the above-mentioned steps, the final summary recommendations were completed and submitted to the WHO Guideline Review Committee for approval in August 2010.

The current Rapid Advice will be reviewed (or incorporated in the full Guidance review) within 12 months, unless significant new evidence emerges before that time to warrant an earlier review process.

3.3 Publication and timing

This *Rapid advice: treatment of tuberculosis in children* will be published online in English. Translation into other official WHO languages will be done by WHO regional offices and partners.

It is anticipated that the 2nd edition of the full Guidance will be available in 2011 for final clearance. Publication and dissemination is estimated to start in 2011. The guidelines target policy-makers and decision-makers at national level, programme managers, and managers responsible for designing and implementing national tuberculosis control programmes for the management of tuberculosis in children.

4. Dissemination, adaptation, implementation and evaluation

WHO works closely with WHO regional and country offices, other United Nations organizations, the Stop TB Partnership and other implementing partners to plan for rapid dissemination, adaptation and implementation of the new recommendations. Much experience has been obtained from previous guidelines on tuberculosis, and active support for revision of guidelines is needed at the country level. These activities will be implemented by WHO's regional and country offices in collaboration with technical partners and the Childhood TB sub-working group of the Stop TB Partnership.

The primary target audiences for this guideline are the managers and staff of national tuberculosis control programmes, together with other providers of tuberculosis care for children, working in public and private health-care facilities at the central, provincial and peripheral levels.

The principal purpose of these guidelines is to help national programmes in setting treatment policies for managing tuberculosis in children. Their further purpose is to guide clinicians working in both the public and private sectors.

Key steps in the dissemination include:

- release of the Rapid advice;
- production and publication of the 2nd edition of the full Guidance, with translation into other languages;
- rapid development of adaptation and transition tools;
- briefings and joint planning for dissemination with international and national implementing partners;
- regional and national conferences and training workshops, to support country adaptation (implemented by WHO's regional and country offices in collaboration with technical partners working in the field of childhood tuberculosis).

Adaptation and transition tools are designed to:

- assist countries in prioritizing limited resources to facilitate full implementation over time;
- avoid compromising access to antituberculosis medicines or exclude access by those most in need;
- prevent disruption of existing efforts to scale up activities related to childhood tuberculosis or threaten adherence to treatment;
- move progressively towards adopting all recommendations.

5. Companion documents

Simple tools to accompany the guideline are being developed by WHO in collaboration with key implementing partners. These tools are designed to:

- assist countries in the revision of national guidelines for the treatment of tuberculosis in children; and
- support the implementation and use of the new higher dosage regimens taking into account the resources and limitations within the country.

The first of these important tools is this Rapid Advice.

6. Collaboration with external partners

There are no external collaborators specific to this Rapid Advice. However, several partners have been engaged in the development of the guideline.

Funding to support this work comes from the Stop TB Partnership's funds for the work of the Childhood TB sub-working group and the budget of WHO's Department of Essential Medicines and Pharmaceutical Policies.

7. Key recommendations

Recommendation 1

Given the risk of drug-induced hepatotoxicity, WHO recommends the following dosages of antituberculosis medicines for the treatment of tuberculosis in children:

isoniazid (H) – 10 mg/kg (range 10–15 mg/kg); maximum dose 300 mg/day
rifampicin (R) – 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day
pyrazinamide (Z) – 35 mg/kg (30–40 mg/kg)
ethambutol (E) – 20 mg/kg (15–25 mg/kg)

(Strong recommendation, moderate-quality evidence)

Remarks

The panel noted the absence of high-quality evidence available to directly assess the risk of drug-induced hepatotoxicity using the new recommended dosages of antituberculosis medicines in children. However, the panel took account of:

- the long duration of clinical experience with these medicines for the treatment of tuberculosis in adults and children;
- a relatively large quantity of low-quality observational studies carried out in a variety of settings and paediatric populations that show no evidence of increased toxicity with dosages of these medicines;
- the potential risk of inefficacy of treatment if lower dosages are used;
- the risk of developing isoniazid resistance if lower dosages are used;
- the relationship between mean inhibitory concentration of the medicines in adults and efficacy outcomes;
- the development of metabolic pathways that increase the metabolism in young children;
- the high likelihood of reporting bias that would over-report the occurrence of hepatotoxicity.

Recommendation 2

Children living in settings where the prevalence of the HIV is high[1] or where resistance to isoniazid is high, or both, with suspected or confirmed pulmonary tuberculosis or peripheral lymphadenitis; or children with extensive pulmonary disease living in settings of low HIV prevalence or low isoniazid resistance, should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months at the following dosages:

isoniazid (H) – 10 mg/kg (range 10–15 mg/kg); maximum dose 300 mg/day
rifampicin (R) – 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day
pyrazinamide (Z) – 35 mg/kg (30–40 mg/kg)
ethambutol (E) – 20 mg/kg (15-25 mg/kg)

(Strong recommendation, moderate-quality evidence)

[1] Defined as countries, subnational administrative units, or selected facilities, where the HIV prevalence among adult pregnant women is ≥1% or among TB patients is ≥5%.

Recommendation 3

Children with suspected or confirmed pulmonary tuberculosis or tuberculous peripheral lymphadenitis who live in settings with low HIV prevalence or low resistance to isoniazid and children who are HIV-negative can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug (HR) regimen for 4 months at the following dosages:

> isoniazid (H) – 10 mg/kg (range 10–15 mg/kg); maximum dose 300 mg/day
> rifampicin (R) – 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day
> pyrazinamide (Z) – 35 mg/kg (30–40 mg/kg)

(Strong recommendation, moderate-quality evidence)

Recommendation 4

Children with suspected or confirmed pulmonary tuberculosis or tuberculous peripheral lymphadenitis living in settings with high HIV prevalence (or with confirmed HIV infection) should not be treated with intermittent regimens (that is, twice-weekly or thrice-weekly doses).

(Strong recommendation, low-to-moderate-quality evidence against the use of intermittent treatment in children)

Remarks

The panel noted that in the systematic review comparing intermittent dosing of medicines with the daily treatment regimens, there were no high-quality studies of intermittent (thrice-weekly) treatment regimens in children. There is some evidence that twice-weekly intermittent regimens are inferior to daily regimens in children. The metabolism of these medicines in children makes it more likely that intermittent regimens may result in inadequate exposure to the medicines, therefore increasing the risk of inefficacy. This evidence is supported by evidence from adult studies where adult patients using intermittent therapy have a higher risk of treatment failure and developing multidrug-resistant tuberculosis.

Recommendation 5

During the continuation phase of treatment, thrice-weekly regimens can be considered for children known to be HIV-uninfected living in settings with well-established directly-observed therapy (DOT).

(Weak recommendation, very low-quality evidence for use of intermittent treatment in children in specific settings)

Remark

The panel noted that, in some regions and countries, there is considerable clinical evidence of success using thrice-weekly intermittent regimens. Recommending changing the well-established practice may result in excluding children from DOT. However, this should only be considered in settings with a low HIV prevalence and a well-established DOT programme.

Recommendation 6

Infants (aged 0–3 months) with suspected or confirmed pulmonary tuberculosis or tuberculous peripheral lymphadenitis should be promptly treated with the standard treatment regimens, as described above.

(Strong recommendation, low-quality evidence)

Remarks

Treatment may require adjustment of dosages to reconcile the effect of age and possible toxicity in young infants. The decision to adjust dosages should be taken by a clinician experienced in managing paediatric tuberculosis.

The panel noted the very limited systematic clinical data describing treatment and outcomes of the treatment of tuberculosis in this age group. The panel took account of:

- the importance of treating tuberculosis in infants as a serious infectious disease with a high morbidity and mortality in this age group;
- the importance of commencing treatment with an effective treatment regimen as soon as the diagnosis of tuberculosis is suspected;
- the need for simplified treatment instructions for programmes dealing with these children.

Recommendation 7

Streptomycin should not be used as part of first-line treatment regimens for children with pulmonary tuberculosis or tuberculous peripheral lymphadenitis.

(Strong recommendation, moderate-quality evidence)

Remarks

The panel noted the low-to-moderate-quality evidence of the efficacy of streptomycin in children and took into account the risk of toxicity associated with the use of streptomycin. Also considered were problems with injection-based treatment regimens and the availability of safer, more effective and oral alternatives. Streptomycin should be reserved for the treatment of multi-drug resistant tuberculosis in children with known drug susceptibility to this medicine.

Recommendation 8

Children with suspected or confirmed tuberculous meningitis should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months; the total duration of treatment being 12 months. The dosages recommended for the treatment of tuberculous meningitis are the same as those described for pulmonary tuberculosis.

(Strong recommendation, low-quality evidence)

Remarks
The panel noted the following:

- there are many observational studies of the treatment of tuberculous meningitis in children, but these are of very low quality;
- the existence of a number of treatment guidelines recommending longer durations of treatment (between 9 months and 2 years);
- high mortality and morbidity associated with tuberculous meningitis (in particular grade 2 and grade 3 tuberculous meningitis);
- that 30% of children with a miliary picture on chest radiography have central nervous system involvement and should be treated with a 12-month regimen.

The panel recommended that the upper end of the recommended dosage range should be considered, given the uncertain penetration of antituberculosis medicines into the central nervous system.

Recommendation 9

Children with suspected or confirmed osteoarticular tuberculosis should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 10 months; the total duration of treatment being 12 months. The doses recommended for the treatment of osteoarticular tuberculosis are the same as those described for pulmonary tuberculosis.

(Strong recommendation, low-quality evidence)

Remarks
The panel noted that although the evidence is of low quality, the treatment regimens used in children were generally given for at least 12 months duration; the studies reported “no relapse” as the main outcome, although the duration of follow-up was often poorly reported. The panel took into account the pharmacological arguments to support the longer duration of treatment for infections of bones and joints and the lack of evidence to indicate an increased risk of toxicity associated with increased duration of treatment and the difficulty of determining cure in patients treated for osteoarticular tuberculosis.

Recommendation 10

Children with proven or suspected pulmonary tuberculosis or tuberculous meningitis caused by multiple drug-resistant bacilli can be treated with a fluoroquinolone in the context of a well-functioning MDR-TB control programme and within an appropriate MDR-TB regimen. The decision to treat should be taken by a clinician experienced in managing paediatric tuberculosis.

(Strong recommendation, very low-quality evidence)

Remarks
The panel noted the lack of long-term safety data for the use of fluoroquinolones in children and the paucity of evidence for their use in the treatment of tuberculosis in children. The panel considered indirect evidence from the treatment of cystic fibrosis and osteomyelitis, which indicated that longer-term use was not associated with an increased risk of joint abnormalities in children. Where arthralgia has been described in studies, it has been completely reversible. The panel took into account the

pharmacological arguments for the use of fluoroquinolones, such as their good penetration of tissue and oral bioavailability and predictable pharmacokinetics in children. The panel reached a consensus that in the context of multi-drug resistant tuberculosis, the benefits of treatment outweighed the risks.

8. Research needs

The needs for research in the field of tuberculosis in children are substantial.

During the guideline review process, the areas where the evidence was insufficient or inadequate were highlighted and the following research needs were identified:

- a randomized trial of different lengths of treatment of tuberculous meningitis;
- a large population-based pharmacokinetics study of all four first-line medicines at the newly recommended dosages, including in children with HIV;
- high-quality observational studies to evaluate the risk of hepatotoxicity of isoniazid at the increased dose of 10 mg/kg;
- pharmacokinetic studies in infants of rifampicin, isoniazid and pyrazinamide;
- a randomized trial or high-quality observational studies to define optimal preventive chemotherapy in children in contact with a confirmed source case of multidrug-resistant tuberculosis.

It is hoped that this revised guideline will act as a stimulus to researchers and funding agencies to encourage, plan and support randomized controlled studies in the field of childhood tuberculosis. In view of the importance of pharmacogenetics in the host and potential genetic differences in *Mycobacterium tuberculosis* populations, such studies should, where possible, be multicentre and enroll children over a spectrum of ages.

9. Members of the Guidelines Group

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11. Declarations of interest

Participants of the meeting for the revision of guidelines for national tuberculosis control programmes on the management of tuberculosis in children reported the following:

Dr Kalle Hoppu reported having been a consultant for Lundbeck A/S Denmark (2007). Dr Hoppu also reported receiving lecture fees from Norit Pharmaceuticals Netherlands, Leiras Ltd. Finland (2008) and Oy Swedish Orphan Ab Finland (2008, 2009) and a fee for providing a written clinical expert opinion for a regulatory submission on behalf of Oy Leiras Finland Ab (2008). He also received expenses from the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), for attending the 10th Commonwealth Pharmacists Association Conference in Ghana, as a speaker invited by the organizers (2009).

Professor Cleotilde How reported being a technical advisor for TBLink, a nongovernmental organization (2008) and receiving non-monetary support from the Philippine Pediatric Society, Inc., for work related to tuberculosis (2009 to date).

Dr Gregory Kearns reported providing consultancy services for Abbott, Wyeth Pharmaceuticals, Cubist Pharmaceuticals, Proctor and Gamble, Tyco Healthcare, Mannkind Pharmaceuticals, Nextwave Pharmaceuticals and Centocor. In addition, Dr Kearns reported that his employer holds research contracts related to child health with the private sector and the United States National Institutes of Health. He also serves as a member of the United States Food and Drug Administration Clinical Pharmacology Advisory Committee, and provides consultation to the National Institutes of Health regarding paediatric drug development and the United States Centers for Disease Control and Prevention related to studies of Rifapentine. Dr Kearns received a fee from WHO to undertake a review of fluoroquinolone use in paediatrics for this meeting.

Dr Robert Gie, Dr Nicola Magrini, Dr Charles Mwansambo, Dr Iveta Ozere and Dr Mary Reichler reported no interest in relation to the meeting.

None of the companies listed in the declarations of interest above make any of the generic products, nor do they make any competitor products. None of the decisions of the panel could have any impact on share prices or sales of the companies named.

Therefore, according to the WHO standards, the Secretariat made the assessment that none of the interests declared were a conflict.

The members of the External Review Group reported no interest in relation to the draft document submitted for their review.


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