9 December 2020

To the WHO EML secretariat,

We are writing to you to set out our proposals for changes to the content of the current EML/EMLChildren (EMLc) and electronic EMLc (eEMLc) in the section, 'Joint Diseases in Children' (section 29)'.

1. **We propose that the following medicines appear under the search term of 'JIA' in the eEMLc and also to appear in the EML/EMLc section 'Joint Diseases in Children'. These medicines have already been approved by the WHO for use in joint diseases in children and we explain further why changes to the current EML/EMLc section 'Joint Diseases in Children' are needed.**

    - **Methotrexate**
    - **Hydroxychloroquine**
    - **Adalimumab**
    - **Certolizumab**
    - **Etanercept**
    - **Golimumab**
    - **Infliximab**
    - **Acetylsalicylic acid**

2. **We also submit applications for three new medicines to be added to the Complementary list in the EML, EMLc and eEMLc - section 'Joint Diseases in Children'. These applications are submitted individually using the template provided by WHO:**

    - **Tocilizumab (anti-IL6)**
    - **Triamcinolone hexacetonide**
    - **Anakinra (anti-IL1)**

These proposals and applications have been collated by our team of individuals (listed below) from the Paediatric Global Musculoskeletal Task Force. We gratefully acknowledge support and guidance from the WHO EML team (Bernadette Cappello and Dr Lorenzo Moja). In preparation for our submissions we have engaged widely with the paediatric rheumatology community around the world. We have many letters of support from professional bodies and parent/family organisations (Appendix 1). In addition we have completed an e-survey to guage opinion about what medicines should be included in the EML/EMLc/eEMLc. This survey has been accepted for publication as a letter in the Pediatric Rheumatology Journal and is in press – we include the letter (Appendix 2).

We acknowledge the significant importance of the WHO EML/EMLc/eEMLc to inform countries around the world about the minimum medicine items necessary to meet the most important priority health needs of populations. We believe that our proposed changes will be very impactful to improve access to medicines to treat children with arthritis around the world and will greatly support clinicians working to improve the clinical care for these children. We are committed to working further with the WHO EML team to facilitate these changes.

We look forward to hearing further from you.

Yours sincerely,

Professor Helen Foster, FRCPCH, FRCP, MD, DCH, Cert Med Ed, MBBS (Hons)
Chair of the Paediatric Global Musculoskeletal Task Force
Strategic Research Advisor and Professor of Paediatric Rheumatology
Newcastle University, UK
h.e.foster@newcastle.ac.uk

Professor Christiaan Scott, MBChB
Co-Chair Paediatric Global MSK Task Force
Associate Professor Paediatric Rheumatologist
Red Cross War Memorial Children's Hospital
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University Hospitals Bristol NHS Foundation Trust & Translational Health Sciences, University of Bristol, Bristol, UK.
Athimalaipet.Ramanan@UHBristol.nhs.uk

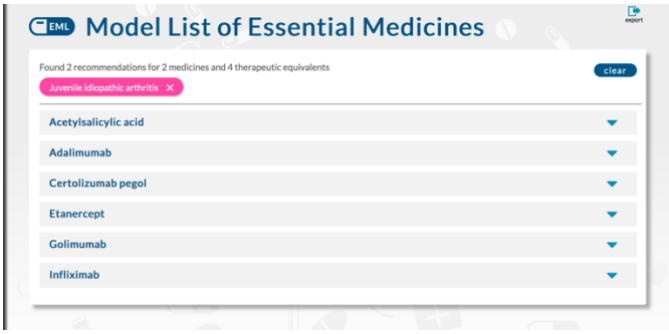
Proposal to amend the structure of 'Joint diseases in Children' sections in the EML/EMLc/eEMLc

We note that a review on the treatment of arthritis in children was requested by the WHO EML Committee in 2009 and was submitted by Dr Peter Gowdie under the supervision of Dr Noel Cranswick. This report reviewed by the Committee in 2011 (WHO Report 965 – excerpts of which we have enclosed – Appendix 3) and page 14 has a summary of the discussions relating to arthritis in children.

https://apps.who.int/iris/bitstream/handle/10665/44771/WHO_TRS_965_eng.pdf;jsessionid=D516A25FA063A94BD54764C238726CCC?sequence=1

We note that the Committee 2011 approved Methotrexate and Hydroxychloroquine for use in Joint disease in children. However, these important recommendations are not clear in subsequent versions of the eEMLc, EML and EMLc as we describe below:

- **In the current eEMLc under the search term JIA (JIA) https://list.essentialmeds.org/?indication=200 (screenshot below) Methotrexate and Hydroxychloroquine are not listed. We suggest clearer metadata links in the search engine so that all approved medicines for in JIA including Methotrexate and Hydroxychloroquine appear in the list. It is especially important that Methotrexate is included as the use of the other approved therapies for JIA (namely the *biological medicines adalimumab, certolizumab, etanercept, golimumab and infliximab) are recommended for use in clinical practice where patients have failed to respond to, or are intolerant of Methotrexate (ACR Guidelines (1)).**



- **In the current EML, section 29.3 'Juvenile Joint Diseases, has listed acetylsalicylic acid (screenshot below). Hydroxychloroquine and Methotrexate and the biological agents (listed above*) are on the Complementary list for 'rheumatoid disorders' (section 29.2). We believe that it would be much clearer if Methotrexate, Hydroxychloroquine and the biological agents were to be also included in 29.3 currently termed 'Juvenile Joint Diseases' under a Complementary list.**

29. MEDICINES FOR DISEASES OF JOINTS	
29.1 Medicines used to treat gout	
allopurinol	Tablet: 100 mg.
29.2 Disease-modifying agents used in rheumatoid disorders (DMARDs)	
chloroquine	Tablet: 100 mg; 150 mg (as phosphate or sulfate).
Complementary List	
azathioprine	*Tablet: 50 mg.*
hydroxychloroquine [c]	*Solid oral dosage form: 200 mg (as sulfate).*
methotrexate	*Tablet: 2.5 mg (as sodium salt).*
penicillamine	*Solid oral dosage form: 250 mg.*
sulfasalazine	*Tablet: 500 mg.*
29.3 Juvenile joint diseases	
acetylsalicylic acid (acute or chronic use)*	*Suppository: 50 mg to 150 mg.* *Tablet: 100 mg to 500 mg.* ** For use for rheumatic fever, juvenile arthritis, Kawasaki disease.*

21st WHO Model List of Essential Medicines (2019) page 51

- **In the current EMLc, section 29 ('Medicines for Diseases of Joints') (screenshot below), Hydroxychloroquine and Methotrexate are listed on the Complementary list but the biological agents (listed above*) are not. We suggest that the biological agents are listed here also on the Complementary list.**

29. MEDICINES FOR DISEASES OF JOINTS	
~~29.1 Medicines used to treat gout~~	
29.2 Disease-modifying agents used in rheumatoid disorders (DMARDs)	
Complementary List	
hydroxychloroquine	*Solid oral dosage form: 200 mg (as sulfate).*

7th WHO Model List of Essential Medicines for Children (2019) page 36

WHO Model List of Essential Medicines for Children 7th edition

methotrexate	*Tablet: 2.5 mg (as sodium salt).*
29.3 Juvenile joint diseases	
acetylsalicylic acid (acute or chronic use)*	*Suppository: 50 mg to 150 mg.* *Tablet: 100 mg to 500 mg.* ** For use for rheumatic fever, juvenile arthritis, Kawasaki disease.*

- **We also suggest that the section 29.2 is renamed as 'Disease Modifying agents used in rheumatic disorders' to aid clarity, rather than 'rheumatoid disorders' given that rheumatoid is a term usually associated with adult rheumatoid arthritis.**

1. Ringold S, AngelesHan ST, Beukelman T, Lovell D, Cuello CA, Becker ML, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for non‐systemic polyarthritis, sacroiliitis, and enthesitis. Arthritis care & research. 2019;71(6):717-34.

APPENDICES (sent collated together into one document)

- Appendix 1 - Letters of support
- Appendix 2 - e-survey (Letter in press), PROJ
- Appendix 3 – WHO TRS 965 report (truncated excerpts)

Appendix 1 – Letters of Support

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

Empowering rheumatology professionals to excel in their specialty

2200 Lake Boulevard NE, Atlanta, GA 30319
Phone: (404) 633-3777 · Fax: (404) 633-1870 · www.rheumatology.org

November 25, 2020

To: Paediatric Global Musculoskeletal Task Force
RE: Submission to revise the WHO Essential Medicines List (EML) for Children

The American College of Rheumatology (ACR), is a global medical society representing over 8,000 adult and peditric rheumatologists, scientists, and rheumatology interprofessional team members worldwide. Our mission is to empower rheumatology professionals to excel in their specialty.

The ACR is very supportive of the application by the Paediatric Global MSK Task Force to revise and update the WHO Essential Medicines List section on 'Joint diseases in children'.

The WHO Essential Medicines List is really important to improve access to medicines and potentially will improve the lives of many children with rheumatic diseases.

Yours sincerely,

David R. Karp, MD, PhD
ACR President
dkarp@rheumatology.org

22nd Asia-Pacific League of Associations for Rheumatology Virtual Congress
24 - 29 October 2020

Sumaira Farman Raja
Professor Rheumatology
National H&MC, FJMU, UHS
Co-Chair Arthritis Care Foundation,
Convener APLAR PaedsRheum SIG

To

Paediatric Global Musculoskeletal Task Force

Nov 24th 2020

Submission to revise the WHO Essential Medicines List (EML) for Children

We are very supportive of the application by the Paediatric Global MSK Task Force to revise and update the WHO EML section on 'Joint diseases in children'.

The WHO EML is really important to improve access to medicines and potentially will improve the lives of many children with rheumatic diseases.

Yours sincerely,

Sumaira Farman, FRCP
FACP, FACR, SCE Rheumatology,
GradCert PRheum
Convener APLAR Paediatric Rheumatology SIG

To

Paediatric Global Musculoskeletal Task Force

24/11/2020

Submission to revise the WHO Essential Medicines List (EML) for Children

We are very supportive of the application by the Paediatric Global MSK Task Force to revise and update the WHO EML section on 'Joint diseases in children'.

The WHO EML is really important to improve access to medicines and potentially will improve the lives of many children with rheumatic diseases.

Yours sincerely,

Christina Boros, MBBS, PhD, FRACP
Chair, Australian Paediatric Rheumatology Group

To: Paediatric Global Musculoskeletal Task Force 23 November 2020

Submission to revise the WHO Essential Medicines List (EML) for Children

We wholeheartedly support the application by the Paediatric Global MSK Task Force to revise and update the WHO EML section on 'Joint diseases in children.'

The WHO EML is crucial to improving access to medicines and potentially will improve the lives of many children with rheumatic diseases.

Yours sincerely,

Catherine McCormack
Executive Director
Arthritis Kids South Africa

CARRA
Childhood Arthritis and Rheumatology Research Alliance

November 26, 2020

To: Paediatric Global Musculoskeletal Task Force
RE: Submission to revise the WHO Essential Medicines List (EML) for Children

The Childhood Arthritis and Rheumatology Research Alliance (CARRA) is a non-profit research network whose mission is to conduct collaborative research to prevent, treat, and cure pediatric rheumatic diseases. CARRA supports research across the T0 to T4 spectrum, as well as workforce development programs, designed to enhance the quality of research and improve the evidence base available for the care and treatment of children with a wide range of rheumatic diseases. Since its inception in 2003, CARRA has grown as an organization and expanded its member base. Currently there are more than 575 members at over 175 pediatric rheumatology sites in the United States and Canada. Our mission is to conduct collaborative research to find the best methods to treat and, ultimately, discover the means to prevent or cure all pediatric rheumatic diseases.

CARRA is very supportive of the application by the Paediatric Global MSK Task Force to revise and update the WHO Essential Medicines List section on 'Joint diseases in children'.

The WHO Essential Medicines List is incredibly important to improve access to medicines and potentially will improve the lives of many children with rheumatic diseases worldwide.

Yours sincerely,

Emily von Scheven, MD, MAS
CARRA President

555 East Wells Street, Suite 1100 | Milwaukee, WI 53202 | 414-918-9822 | info@carragroup.org
www.carragroup.org

To

Paediatric Global Musculoskeletal Task Force

Date 23/11/2020

Submission to revise the WHO Essential Medicines List (EML) for Children

We are very supportive of the application by the Paediatric Global MSK Task Force to revise and update the WHO EML section on 'Joint diseases in children'.

The WHO EML is really important to improve access to medicines and potentially will improve the lives of many children with rheumatic diseases.

Yours sincerely,

Wendy Costello
Chair ENCA
European Network of Children with Arthritis and Auto-inflammatory Diseases

UNIVERSIDADE ESTADUAL PAULISTA
"JÚLIO DE MESQUITA FILHO"
Campus de Botucatu

To

Paediatric Global Musculoskeletal Task Force

November 20th 2020

Submission to revise the WHO Essential Medicines List (EML) for Children

We are very supportive of the application by the Paediatric Global MSK Task Force to revise and update the WHO EML section on 'Joint diseases in children'.

The WHO EML is really important to improve access to medicines and potentially will improve the lives of many children with rheumatic diseases.

Yours sincerely,

Claudia Saad Magalhães MD
Professor of Paediatric Rheumatology
São Paulo State University (UNESP) Brazil

On behalf of the Paediatric Rheumatology Committee
Brazilian Society of Rheumatology
Brazilian Society of Paediatrics
PANLAR Paediatric Rheumatology Study Group

PAEDIATRIC RHEUMATOLOGY EUROPEAN ASSOCIATION

21 November 2020

To: Paediatric Global Musculoskeletal Task Force

Concern: Submission to revise the WHO Essential Medicines List (EML) for Children

We are very supportive of the application by the Paediatric Global MSK Task Force to revise and update the WHO EML section on 'Joint diseases in children'.

The WHO EML is really important to improve access to medicines and potentially will improve the lives of many children with rheumatic diseases.

Yours sincerely,

Prof. Angelo Ravelli, MD
President
Paediatric Rheumatology European Society (PReS)

PAFLAR

Paediatric Society of the African League against Rheumatism

Stronger Together for a Better Future

23rd November 2020

To: Paediatric Global Musculoskeletal Task Force

Re: Submission to revise the WHO Essential Medicines List (EML) for Children

We are very supportive of the application by the Paediatric Global MSK Task Force to revise and update the WHO EML section on 'Joint diseases in children'.

The WHO EML is really important to improve access to medicines and potentially will improve the lives of many children with rheumatic diseases.

Yours sincerely,

Angela Migowa | EPLS|MBCHB|MMED

Chair PAFLAR Core Working Task Force Group

Assistant Professor, Paediatric Rheumatology

Department of Paediatrics and Child Health

Aga Khan University (East Africa)

P.O. Box 30270(00100) - Nairobi, Kenya

angela.migowa@aku.edu

PAFLAR

Stronger Together for a Better Future

Pediatric Rheumatology Society of Thailand

270 Rama VI Rd. Ratchathewi,
Bangkok, Thailand, 10400
Tel: +662-201-0446, Fax: +662-201-0446

To
Paediatric Global Musculoskeletal Task Force

November 21, 2020

Submission to revise the WHO Essential Medicines List (EML) for Children

At present, there is a difficulty to assess some essential medications, including biologic agents and immunosuppressive medications, for the treatment of rheumatic diseases in Thailand. Our government offered the Universal Coverage Scheme (UCS) for Thai people, especially those who have low socioeconomic status, to access to medical care. However, medications that they can access via UCS have to be on the National List of Essential Medicines (NLEM). Biologic agents and some immunosuppressive medications do not include in the NLEM. Due to this problem, some of our patients still have uncontrollable diseases, leading to increasing disability and mortality rates.

Therefore, we are very supportive of the application by the Paediatric Global MSK Task Force to revise and update the WHO EML section on 'Joint diseases in children'. The medications in the WHO EML can lead to update the NLEM in our country in the future.

The WHO EML is really important to improve access to medicines and potentially will improve the lives of many children with rheumatic diseases.

Yours sincerely,

Soamarat

Soamarat Vilaiyuk, MD
Associate Professor of Pediatrics
Chair Pediatric Rheumatology Society of Thailand
Chief of Rheumatology Division, Department of Pediatrics,
Faculty of Medicine Ramathibodi Hospital, Mahidol University
Bangkok, Thailand

Sumaira Farman Raja
Professor Rheumatology
National H&MC, FJMU, UHS
Co-Chair Arthritis Care Foundation,
Convener APLAR PaedsRheum SIG

To

Paediatric Global Musculoskeletal Task Force

Nov 24th 2020

Submission to revise the WHO Essential Medicines List (EML) for Children

We are very supportive of the application by the Paediatric Global MSK Task Force to revise and update the WHO EML section on 'Joint diseases in children'.

The WHO EML is really important to improve access to medicines and potentially will improve the lives of many children with rheumatic diseases.

Yours sincerely,

Sumaira Farman, FRCP
FACP, FACR, SCE Rheumatology,
GradCert PRheum
Convener APLAR Paediatric Rheumatology SIG

SARAA
South African Rheumatism & Arthritis Association

+27 76 276 5930 +27 11 933 9377 kmakan17@gmail.com www.saraa.co.za

24 November 2020

To: Paediatric Global Musculoskeletal Task Force

RE: Submission to revise the WHO Essential Medicines List (EML) for Children

We are very supportive of the application by the Paediatric Global MSK Task Force to revise and update the WHO EML section on 'Joint diseases in children'.

The WHO EML is really important to improve access to medicines and potentially will improve the lives of many children with rheumatic diseases.

Yours sincerely,

Kavita Makan

President

SARAA ENDORSED

UANL

To

Paediatric Global Musculoskeletal Task Force

November 20th, 2020.

Submission to revise the WHO Essential Medicines List (EML) for Children

We are very supportive of the application by the Paediatric Global MSK Task Force to revise and update the WHO EML section on 'Joint diseases in children'.

The WHO EML is really important to improve access to medicines and potentially will improve the lives of many children with rheumatic diseases. This effort will be very helpful to patients from resource-constrained settings in order to expose their needs to local authorities and began a call for action in low- and middle-income countries.

Yours sincerely,

Fernando García Rodríguez, M.D.
Pediatrics Research Coordinator
Associate Professor on Pediatrics and Pediatric Rheumatology
Universidad Autónoma de Nuevo León (UANL), Mexico

DEPARTAMENTO DE PEDIATRIA
Av. Francisco I Madero Pte y Av. Gonzalitoz
Col. Mitras Centro C.P. 64460, Monterrey, N.L. México.
Apartado 1-4459 Tel (81)8348-5221
Tel y Fax: 8346 9959

Departamento de Pediatría
Y ESPECIALIDADES, HOSPITAL UNIVERSITARIO, UANL

30 November 2020

Dear Paediatric Global Musculoskeletal Task Force

Submission to revise the WHO Essential Medicines List (EML) for Children

We are very supportive of the application by the Paediatric Global MSK Task Force to revise and update the WHO EML section on 'Joint diseases in children'.

The WHO EML is really important to improve access to medicines and potentially will improve the lives of many children with rheumatic diseases.

Yours sincerely,

Zoë Chivers

Head of Services
Versus Arthritis

z.chivers@versusarthritis.org

Appendix 2 – e-Survey Letter to the Editor, Pediatric Rheumatology Online Journal

(in press)

Revising the WHO Essential Medicines List for paediatric rheumatology

Chris Scott[1], Nicola Smith[2], Rebecca James[3], Ben Whitehead[3], Rochelle Green[4], Helen Foster[5] on behalf of the Paediatric Global MSK Task Force.

[1]Department of Paediatrics, University of Cape Town, Cape Town, South Africa
[2]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK
[3]Paediatric Rheumatology, Queensland Children's Hospital, Brisbane, Queensland, Australia
[4] Pharmacy, Queensland Children's Hospital, Brisbane, Queensland, Australia
[5]Population and Health Sciences Institute, Newcastle University, Newcastle Upon Tyne, UK.

Corresponding author: h.e.foster@newcastle.ac.uk

Dear Editor,

The World Health Organisation (WHO) Essential Medicines List (EML) [1] informs countries about the minimum medicine items necessary to meet priority health needs of the population and guide national and institutional medicine lists, especially in Low Resource Income Countries. The current EML under medicines for 'joint diseases in children' does not reflect current best practice [2] and an important theme of work from the Paediatric Global Musculoskeletal Health Task Force (TF) [3] is to revise the listing for medicines relevant to paediatric rheumatic diseases.

Healthcare professionals working in paediatric rheumatology and who are TF members were invited to take part in an anonymous online survey WHO EML to explore which drugs they deemed to be 'essential' and 'ideal' for the clinical practice in their context. No reminders to the survey were sent. We had 97 responders, from 43 countries across all continents and mainly from low resource countries (Asia n=51/97). Respondents had a range of 1-35 years of clinical practice and included consultant grade paediatric rheumatologists (n=77), consultant general paediatricians with interest in rheumatology (n=13), paediatric rheumatology trainees (n=3), adult rheumatologists (n=3) and a nurse working in paediatric rheumatology (n=1). Survey data were analysed by applying descriptive statistics and free-text comments were analysed following standard procedures for qualitative analysis [4].

Most respondents (n=70/97, 72%) reported that a revised EML would very likely improve access to medicines in their country, improve drug accessibility within their clinical practice, provide assistance when negotiating with healthcare agencies or insurance companies and

further increase awareness about paediatric rheumatology issues. They deemed that the EML should list the drugs in Table 1; 80% respondents identified 5 agents as ‘essential’ (oral, intra-articular and intravenous corticosteroids, NSAIDS, Hydroxychloroquine and Methotrexate [oral and subcutaneous]) and a wide range of synthetic and biologic DMARDS as well as other immunosuppressive agents be included. This ‘cut off’ of 80% will form the basis of the TF application to the WHO to revise the EML with the submission planned for late 2020. It is our hope that raising awareness and improving access to appropriate therapy will lead to better outcomes for children with rheumatic diseases globally and allow for a targeted treatment approach [5].

Table: Suggested medicines to be included in the WHO EML

Drug	**Should Include (Ideal) (% refers to respondents)**	**Inclusion ‘Essential’**
Oral prednisolone	100%	92%
Oral NSAIDs	99%	93%
Hydroxychloroquine	98%	88%
Intravenous Methylprednisolone	98%	83%
Methotrexate oral	96%	81%
Mycophenolate Mofetil	95%	77%
Azathioprine	94%	71%
Methotrexate subcutaneous	91%	80%
Intravenous cyclophosphamide	91%	77%
Adalimumab	91%	71%
Anakinra	90%	60%
Etanercept	87%	70%
Intra-articular corticosteroid Triamcinolone Hexacetonide	86%	64%
Intravenous Tocilizumab	86%	63%
Oral prednisolone (soluble)	86%	55%
Ciclosporin	85%	52%
Sulphasalazine	84%	51%
Subcutaneous Tocilizumab	81%	46%
Infliximab	80%	52%
Intravenous bisphosphonate (e.g. pamidronate)	76%	37%
Intra-articular corticosteroid Triamcinolone Acetonide	72%	28%
Intra-articular corticosteroid Methylprednisolone	45%	25%
Oral cyclophosphamide	41%	16%
Inhaled analgesia (nitrous oxide)	36%	15%
Thalidomide	34%	8%

Total Respondents: 97

Abbreviations

EML: Essential Medicines List

TF: Paediatric Global Musculoskeletal Task Force

WHO: World Health Organisation

Declarations

Ethics approval and consent to participate

Formal ethical approval was not required. Survey respondents consented to participation through submitting a completed online survey response.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article (and its supplementary information files).

Competing interests

The authors declare they have no competing interests.

Funding:

Not applicable, work was not funded.

Authors' contributions.

The concept and case of need for the survey was led by HF and CS. All authors contributed to the survey content. NS set up the online survey and analysed the data. All authors read and approved the final manuscript.

Acknowledgements

We are grateful to all the Paediatric Global Musculoskeletal Task Force members who participated in the survey.

References

1. The WHO Essential Medicines List 2019 [Available from: https://www.who.int/medicines/publications/essentialmedicines/en/.
2. Foster HE, Scott C. Update the WHO EML to improve global paediatric rheumatology. Nat Rev Rheumatol. 2020;16:123.
3. Foster HE, Scott C, Tiderius CJ, Dobbs MB. The paediatric global musculoskeletal task force-'towards better MSK health for all'. Pediatr Rheumatol. 2020;18(1):1-3.
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Appendix 3 - WHO Technical Report Series 965

WHO Technical Report Series

965

The Selection and Use of Essential Medicines

Report of the WHO Expert Committee, 2011
(including the 17th WHO Model List of Essential Medicines
and the 3rd WHO Model List of Essential Medicines for Children)

World Health Organization

The World Health Organization was established in 1948 as a specialized agency of the United Nations serving as the directing and coordinating authority for international health matters and public health. One of WHO's constitutional functions is to provide objective and reliable information and advice in the field of human health, a responsibility that it fulfils in part through its extensive programme of publications. The Organization seeks through its publications to support national health strategies and address the most pressing public health concerns of populations around the world. To respond to the needs of Member States at all levels of development, WHO publishes practical manuals, handbooks and training material for specific categories of health workers; internationally applicable guidelines and standards; reviews and analyses of health policies, programmes and research; and state-of-the-art consensus reports that offer technical advice and recommendations for decision-makers. These books are closely tied to the Organization's priority activities, encompassing disease prevention and control, the development of equitable health systems based on primary health care, and health promotion for individuals and communities. Progress towards better health for all also demands the global dissemination and exchange of information that draws on the knowledge and experience of all WHO's Member countries and the collaboration of world leaders in public health and the biomedical sciences. To ensure the widest possible availability of authoritative information and guidance on health matters, WHO secures the broad international distribution of its publications and encourages their translation and adaptation. By helping to promote and protect health and prevent and control disease throughout the world, WHO's books contribute to achieving the Organization's principal objective – the attainment by all people of the highest possible level of health.

The WHO Technical Report Series makes available the findings of various international groups of experts that provide WHO with the latest scientific and technical advice on a broad range of medical and public health subjects. Members of such expert groups serve without remuneration in their personal capacities rather than as representatives of governments or other bodies; their views do not necessarily reflect the decisions or the stated policy of WHO. An annual subscription to this series, comprising about four to six such reports, costs CHF 150.00/US$ 180.00 (CHF 105.00/US$ 126.00 in developing countries). For further information, please contact: WHO Press, World Health Organization, 20 avenue Appia, 1211 Geneva 27, Switzerland (tel. +41 22 791 3264; fax: +41 22 791 4857; e-mail: bookorders@who.int; order on line: http://www.who.int/bookorders).

WHO Technical Report Series

The Selection and Use of Essential Medicines

Report of the WHO Expert Committee, 2011
(including the 17th WHO Model List of Essential Medicines
and the 3rd WHO Model List of Essential Medicines for Children)

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization

World Health Organization

WHO Library Cataloguing-in-Publication Data:

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(WHO technical report series ; no. 965)

1. Essential drugs - administration and dosage. 2. Drug information services. 3. Drug utilization. 4. Child. I. World Health Organization. II. Series.

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Contents

Executive summary

The 18th Meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines took place in Accra, Ghana on 21–25 March 2011. This was the first meeting of the Committee held outside of Geneva. The purpose of the meeting was to review and update the WHO Model List of Essential Medicines (EML) as well as the WHO Model List of Essential Medicines for Children (EMLc). The Expert Committee Members and Temporary Advisers who participated in the meeting are listed in the report, together with their declarations of interest.

In accordance with its approved procedures (http://apps.who.int/gb/archive/pdf_files/EB109/eeb1098.pdf) the Expert Committee evaluated the scientific evidence on the comparative effectiveness, safety and cost–effectiveness of medicines to update the WHO Model List of Essential Medicines and the Model List of Essential Medicines for Children. The Expert Committee:

- approved the addition of 16 new medicines to the EML;
- approved the deletion of 13 medicines from the EML;
- approved new indications for 4 medicines already listed on the EML;
- approved the addition of a new dosage form or strength for 4 medicines already on the EML;
- rejected 9 applications for the addition of a medicine to EML;
- approved the addition of 16 new medicines to the EMLc;
- approved the deletion of 15 medicines from the EMLc;
- rejected 3 applications for the addition of a new medicine to the EMLc.

Some of the main recommendations made, in order of their appearance on the Model List, were:

- Section 6: addition of artesunate + amodiaquine combination tablet for the treatment of malaria in adults and children, in line with current WHO treatment guidelines. In making its decision, the 2011 Committee reviewed the latest clinical evidence and the information about licensing in several countries of the fixed-dose combination tablet. The Committee noted, however, that appropriate doses of both medicines can also be achieved using combinations of the mono-component products, including co-blistered presentations.
- Section 10: addition of tranexamic acid injection for the treatment of adult patients with trauma and significant risk of ongoing haemorrhage. On the basis of the results of a very large trial of the

use of tranexamic acid specifically for trauma patients — including those who have been in road traffic accidents, the Committee concluded that there is sufficient evidence to support the proposal that listing tranexamic acid may contribute to a reduction in this cause of death.

- Section 18.5: addition of glucagon injection, 1 mg/ml to treat acute severe hypoglycaemia in patients with diabetes, to support efforts in many countries to ensure appropriate treatment of the increasing number of patients with diabetes. The Committee also recommended that careful attention be paid to the cost of procuring glucagon and noted that based on the experience with other high-cost medicines, such as the antiretrovirals, inclusion in the EML may help reduce prices.
- Section 22.1: addition of misoprostol tablet, 200 micrograms for the prevention of postpartum haemorrhage, where oxytocin is not available or cannot be safely used. WHO guidelines currently recommend that *in situations where there is no other treatment available*, misoprostol can be used to prevent and treat postpartum haemorrhage due to uterine atony. New evidence submitted to the Committee shows that misoprostol can be safely administered to women to *prevent* postpartum haemorrhage by traditional birth attendants or assistants trained to use the product at home deliveries. Misoprostol should *not*, however, be used *to treat* haemorrhage unless there is no other option available (see below). Moreover, if it is available, oxytocin is recommended as it is more effective and cheaper.

Other medicines that were added to the Model List are: isoflurane, propofol, midazolam, clarithromycin, miltefosine, paclitaxel and docetaxel, bisoprolol, terbinafine cream/ointment, mupirocin cream/ointment, and atracurium.

The Expert Committee did not approve the following proposals for addition of medicines on the basis of the evidence submitted: ether, gatifloxacin, a fixed-dose combination of isoniazid + pyridoxine + sulfamethoxazole + trimethoprim (because there is no marketed product), etravirine, darunavir, raltegravir, dihydroartemisinin + piperaquine, pyronaridine + artesunate, loperamide and misoprostol tablet for treatment of postpartum haemorrhage.

The Expert Committee also assessed a review of the comparative effectiveness and cost–effectiveness of analogue insulins compared to recombinant human insulin. The products considered were: insulin glargine, insulin detemir, insulin aspart, insulin lispro, and insulin glulisine. The Committee noted that while many of the comparative trials find a statistically

significant difference between analogue insulins and standard recombinant human insulin for some effects on blood glucose measurements, there is no evidence of a clinically significant difference in most outcomes. The Committee concluded that insulin analogues currently offer no significant clinical advantage over recombinant human insulin and there is still concern about possible long-term adverse effects.

A summary of reasons for all changes to the List is in Section 1 of the report. All applications and documents considered by the Committee will remain available on the web site for the meeting at: http://www.who.int/selection_medicines/committees/expert/18/en/index.html.

List of participants of the 18th Expert Committee on the Selection and Use of Essential Medicines

Members:

Professor Hany Abdel-Aleem, Department of Obstetrics and Gynecology, Women Health Centre, Assiut University Hospital, Assiut, Egypt

Dr Lisa A Bero, Professor, University of California, San Francisco, USA

Professor Abdol Majid Cheraghali, Iranian Blood Transfusion Organization, Hemmat Highway, Tehran, Islamic Republic of Iran

Professor Noël Cranswick, Clinical Pharmacologist, Royal Children's Hospital, Parkville, Victoria, Australia

Professor Rohini Fernandopulle, Senior Lecturer, Department of Pharmacology, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka

Mr Andy Gray, Department of Therapeutics and Medicines Management, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Congella, South Africa

Dr Kalle Hoppu, Director, Poison Information Centre, Helsinki University Central Hospital, Helsinki, Finland

Dr Gregory L Kearns, Professor of Pediatrics and Pharmacology, University of Missouri Kansas City (UMKC), Kansas City, USA (by telephone)

Professor David Ofori-Adjei, Professor of Tropical Clinical Pharmacology, Professor of Medicine & Therapeutics, Noguchi Memorial Institute for Medical Research, University of Ghana, Accra, Ghana

Dr Lenita Wannmacher, former Professor of Clinical Pharmacology, Faculty of Medicine, Federal University of Rio Grande do Sul, Brazil and Consultant and Senior Lecturer on Selection and Rational Use of Medicines for the Brazilian Ministry of Health and the National Health Vigilance Agency, Porto Alegre, Brazil

Professor Anita Zaidi, Associate Professor, Department of Pediatrics and Microbiology, Aga Khan University, Karachi, Pakistan

Temporary Advisers:

Dr Agnès Saint Raymond, European Medicines Agency, London, United Kingdom

Professor Jennifer Welbeck, Department of Child Health, University of Ghana Medical School, Korle Bu Teaching Hospital, Accra, Ghana

Agencies:

UNICEF

Mr Henrik Nielsen, Technical Specialist, Essential Medicines and Nutrition Centre, UNICEF Supply Division, The United Nations Children's Fund (UNICEF), Copenhagen, Denmark

UNFPA

Dr Kabir U Ahmed, Technical Adviser, Commodity Security Branch, Technical Division, United Nations Population Fund (UNFPA), New York, USA

Region:

Dr Analia Porrás, Advisor, Medicines and Technology, HSS/MT (Region of the Americas/ Pan American Health Organization)

WHO Country Office/Ghana:

Dr Daniel Kertesz, WHO Representative to Ghana

Mrs Edith Andrews Annan, Country Adviser-Essential Medicines, World Health Organization, Accra, Ghana

WHO HQ/Secretariat:

Dr Clive Ondari, Coordinator, MAR
Dr Suzanne Hill, Secretary of the Expert Committee, MAR
Dr Anna Ridge, MAR
Ms Monique Renevier, MAR

Declaration of interests of Members of the 18th Expert Committee on the Selection and Use of Essential Medicines

Members reported the following interests:

Professor Noël Cranswick reported receiving honoraria and travel expenses (including economy airfares) from GlaxoSmithKline to produce guidelines and present to multiple audiences on the use of antipyretic medicines in fever and to act as a consultant on the use of paracetamol in children. He was therefore asked to contribute to the discussions but not to any recommendations related to the use of ibuprofen in children.

Mr Andy Gray reported having accepted travel support from Aspen Pharmacare and Fresenius Kabi to attend continuing education events as a guest speaker, and receiving research support grants from Gilead Sciences and various donors of antiretroviral medicines used in AIDS Clinical Trials Group (ACTG) and International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) trials. He reported being a member of the Scheduling and Naming Expert Committee of the South African Medicines Control Council; being a past director of a government funding agency for biotechnology and a non-executive director of a non-profit-making company engaged in the development and implementation of information technology-based health care solutions for the developing world. He was therefore asked not to contribute to recommendations on antiretrovirals.

Dr Kalle Hoppu reported receiving lecture fees from Oy Swedish Orphan AB, Norit Pharmaceuticals, and a consultancy fee from Oy Leiras Finland AB for providing a written clinical expert opinion for a regulatory submission.

Dr Gregory L Kearns reported receiving research grants from the National Institute of Health, the Pediatric Trials Network, MPEX Pharmaceuticals, and Johnson & Johnson; he also declared being a member of the Center for Drug Evaluation for the US Food and Drug Administration Advisory Committee.

Professor Anita Zaidi reported a significant research interest in the management of typhoid fever, and had been the senior author of Cochrane systematic reviews on this topic. She also reported support from the Novartis Vaccine Foundation to her department, for studies on the immunogenicity of conjugate typhoid vaccine.

Professor David Ofori-Adjei reported being the team leader for monitoring and evaluation of a Pfizer-sponsored mobilize against malaria project in Ghana. He was asked not to contribute to recommendations on antimalarials.

Professor Hany Abdel-Aleem, Dr Lisa A Bero, Professor Abdol Majid Cheraghali, Professor Rohini Fernandopulle, and Dr Lenita Wannmacher reported no conflicts of interest.

Temporary Advisers reported the following interests:

Dr Agnès Saint-Raymond reported being a full-time employee of the European Medicines Agency.

Professor Jennifer Welbeck reported no conflict of interest.

1. Introduction

The 18th meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines was held from 21 to 25 March 2011, in Accra, Ghana.

The meeting was opened by the WHO Representative in Ghana on behalf of the Director-General of the World Health Organization (WHO). The WHO Representative noted that this is the first time a WHO Expert Committee has met outside of Geneva and thanked the Ghana Ministry of Health for agreeing to allow the meeting to be held in Accra.

The WHO Representative noted that Expert Committee members are selected from panels of experts that are nominated from many organizations and governments. Expert Panel and Committee members are required to provide advice as individuals, however, and may not take directions from any external organization or government.

Dr Clive Ondari welcomed members on behalf of the Department of Essential Medicines and Pharmaceutical Policies and noted that this was an unique event, being the first Expert Committee meeting to be held outside of WHO Headquarters in Geneva.

2. Open session

The open session was attended by a variety of interested parties, as well as representatives and observers from the Ghana Ministry of Health. The Secretariat provided a brief update on activities since the last meeting of the Expert Committee and highlighted issues to be addressed during the 18th Expert Committee meeting.

The following comments on agenda items were noted.

1. Comments were submitted in writing by Médecins Sans Frontières on malaria treatment, miltefosine, succimer, antiretroviral medicines, neglected diseases in children, and on the treatment of tuberculosis (TB) in children. An additional comment on the last subject was also submitted.
2. A statement of support on the inclusion of misoprostol for the prevention of postpartum haemorrhage, presented by Professor SWK Adadevoh (Ghana).

The following additional comments from participants were provided to the Committee.

1. A statement of support for the inclusion of misoprostol for the prevention of postpartum haemorrhage, by Professor A Gessessew (Ethiopia).

5. Applications only for paediatric medicines

Section 2: Analgesics, antipyretic medicines, non-steroidal anti-inflammatory medicines (NSAIMs), medicines used to treat gout, and disease-modifying agents in rheumatoid disorders (DMARDs)

Section 2.1: Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)

Ibuprofen (review) – Children

At its 2009 meeting, the Committee requested a review of ibuprofen use in children for the treatment of fever and pain. The current EMLc includes ibuprofen, as tablet, for the treatment of pain and fever in infants aged more than 3 months, and for the treatment of acute attacks of migraine, and ibuprofen as oral liquid or tablet for palliative care (treatment of bone pain). A review was prepared for the Committee by Mr Andy Gray, University of KwaZulu-Natal, South Africa. Expert reviews were provided by Dr Lisa A Bero and Professor Anita Zaidi.

The Committee noted that the review included evidence from three systematic reviews and RCTs in the treatment of pain and fever. The Committee considered the first systematic review (*2*) which analysed efficacy and safety data for both ibuprofen and paracetamol in children and adults. Based on English language publications only, there were 18 prospective or retrospective studies in infants, children, and adolescents. Eleven studies found no difference in analgesic efficacy between paracetamol and ibuprofen and seven reported superiority for ibuprofen. The estimate of standardized mean difference in pain measurement was 0.28 (95% CI 0.1–0.46) in favour of ibuprofen (within 2 hours of dosing).

The effect on fever was analysed in 30 studies; 15 concluded that ibuprofen was superior to paracetamol and 15 showed no difference. The Committee noted that of the 7 RCTs involving 576 participants, only 1 included children aged 2 to 14 years. The estimate of standardized mean difference in fever from these seven trials was 0.26 (95% CI 0.1–0.41) in favour of ibuprofen (within 4 hrs of dosing).

Two additional studies were considered to identify the benefit of either paracetamol or ibuprofen as antipyretics. One was a meta-analysis of animal studies of antipyretics used in influenza (*3*), which suggested an increase in mortality in influenza-infected animals associated with antipyretic use (OR 1.34; 95% CI 1.04–1.73). The second study, a RCT of antipyretics in 231 children aged 4 months to 4 years (mean 1.7 years) showed no efficacy of antipyretics on the prevention of febrile seizures, and no efficacy on fever accompanying febrile seizures. The trial used maximum recommended doses of antipyretics (rectal diclofenac or placebo as first line, then oral ibuprofen, paracetamol, or

placebo) and confirmed previous data on the lack of efficacy on febrile seizures prevention (*4*).

The Committee also considered the evidence of safety from 31 studies from the systematic review (*2*). A single trial concluded that paracetamol was better tolerated and all others showed no difference between paracetamol and ibuprofen. A review (*5*) of 24 RCTs and 12 observational studies showed no significant difference between ibuprofen and paracetamol for adverse events requiring discontinuation, and systemic reactions (RR 0.54; 95% CI 0.17–1.71 and RR 1.03; 95% CI 0.98–1.10, respectively).

The Committee considered that the short use of ibuprofen in these indications may explain the lack of toxicity, as NSAIMs toxicity is increased by longer-term use, higher doses, and increased age and paracetamol liver toxicity is due to overdosing (intentional or not).

Asthma-related symptoms were specifically analysed by Kanabar et al. (*6*), who concluded that there might be a protective effect of ibuprofen compared to paracetamol.

The Committee noted that the median cost of a 100-ml bottle of paracetamol is US$ 0.39 while that of ibuprofen would be US$ 0.87. The Committee also noted that the new WHO treatment guidelines on the management of persistent pain in children include recommendations for use of ibuprofen.

The Committee noted that administration of antipyretics is established practice, but that there is no compelling evidence of clinical benefit from the treatment of fever. There is concern that reduction of fever may itself be associated with possible harm. The Committee also noted that there may be adverse effects associated with either paracetamol or ibuprofen, and therefore decisions to treat fever in children would need to take account of the trade-off between benefits and harms.

The Committee recommended including ibuprofen suspension (200 mg/5 ml) for the treatment of pain as a safe alternative to paracetamol, noting that there are no data to support its use in infants aged less than 3 months. The Committee noted the need for flexible oral solid dosage forms, suitable for children, but decided to list the oral liquid form at this time, due to availability and cost.

Section 2.2: Opioid analgesics

Codeine (deletion) – Children

An application was prepared by Dr Barbara Milani, Technical Officer, Department of Essential Medicines and Pharmaceutical Policies, WHO Secretariat, for the deletion of codeine from Section 2.2 of the Model List of Essential Medicines for Children.

An expert review was prepared by Professor Abdol Majid Cheraghali.

The Committee was informed that the WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses have recently been updated. The new guidelines recommend the use of paracetamol or ibuprofen, followed by morphine if pain has not been adequately controlled. Codeine is no longer recommended. The Committee noted that in children aged less than 5 years, the enzyme required to convert codeine to its active metabolite, morphine, is estimated to be no higher than 25% of adult values and as a result the analgesic effect of codeine is low or absent in neonates and young children (*7*). The Committee also noted that there is considerable pharmacogenetic variability among populations; treatment with codeine is ineffective in poor metabolizers and potentially toxic in fast and extensive metabolizers. Codeine therefore should not be regarded as an adequate substitute for morphine. The Committee considered indirect evidence from one RCT (*8*) that suggests codeine is no better than ibuprofen or paracetamol in terms of efficacy and safety for the treatment of musculoskeletal trauma in children.

The Committee therefore recommended the deletion of codeine from Section 2.2 of the Model List of Essential Medicines for Children due to evidence indicating that the analgesic effect is low or absent in neonates and young children; evidence of considerable pharmacogenetic variability among populations, making its efficacy and safety questionable in an unpredictable proportion of the paediatric population; and low-quality evidence indicating that it is not safer or more efficacious than paracetamol or ibuprofen for the treatment of musculoskeletal trauma in children. The Committee also noted the need to improve access to appropriate analgesics, especially morphine, in all settings.

Further, the Committee recommended that the inclusion of codeine 30 mg in the EML for adults be reviewed.

Section 2.4: Disease-modifying agents used in rheumatoid disorders

Methotrexate, sulfasalazine, azathioprine, leflunomide, hydroxychloroquine, mycophenolate, and cyclosporine (review) – Children

At its 2009 meeting, the Committee had requested a review of the medicines needed for the treatment of juvenile idiopathic arthritis (JIA) in children, as it did not endorse any of the medicines currently listed. The current EMLc includes acetylsalicylic acid to treat systemic onset JIA, Kawasaki disease, and rheumatic fever (Complementary List), as well as immunoglobulins (intravenous Ig) for Kawasaki disease.

A review was prepared by P Gowdie (Royal Children's Hospital, Melbourne, Australia) to identify priority rheumatic conditions in children, treatment options, evidence for efficacy and safety, and to make recommendations

for the inclusion of medicines. Professor Rohini Fernandopulle and Dr Lenita Wannmacher provided expert reviews.

The Committee noted that the most frequent condition in children is JIA, with three main forms: systemic onset, polyarticular, and oligo-monoarticular. Other conditions of interest are juvenile dermatomyositis/polymyositis (JDM), and systemic lupus erythematosus (SLE), but these are infrequent in children. Other chronic arthritic diseases affecting children such as acute rheumatic fever, Lyme disease, post-streptococcal reactive arthritis, Kawasaki disease, and other vasculitides were not discussed in the application.

The Committee noted that the following pharmacological classes were used: NSAIMs for the management of symptoms; corticosteroids at immunosuppressive doses (especially for paediatric SLE and JDM); and DMARDs which include methotrexate, cyclophosphamide, azathioprine, cyclosporine, mycophenolate, leflunomide, sulfasalazine, and chloroquine or hydroxychloroquine. DMARDs aim to control disease activity, prevent irreversible organ damage, and decrease the burden of the disease or steroid treatment.

The Committee first considered whether these conditions represent a priority health problem for the population. Estimates of prevalence are available for JIA in developed countries (from 7 to 401 per 100 000 children) and this condition can produce a high burden of disease if it continues into adulthood with severe disability or the need for joint replacement. Juvenile dermatomyositis, on the other hand, is a rare disease and if treated appropriately with high doses of steroids, immunosuppressants and supportive care, can result in little disability. The prevalence of paediatric SLE, a chronic, life-threatening disease, ranges between 0.36 and 0.9 per 100 000 children. The Committee noted the lack of specific data in children affected by chronic arthritis or inflammatory systemic diseases in developing countries.

The Committee evaluated the evidence provided in the review for each of the medicines. A summary of the considerations is provided in Table 1 and full details of the clinical evidence are in the application.

Methotrexate

The Committee noted that the use of methotrexate (MTX) in children requires monitoring, in particular of liver enzymes, on a regular basis. The Committee noted the risk of serious adverse effects associated with inadvertent daily dosing of MTX instead of weekly. Such mistakes can be due to prescribing errors (commonly seen at transfers between sites of care), dispensing errors, and patient errors.

The Committee concluded that methotrexate should be included in the Complementary List of the EMLc, based on the evidence of efficacy and safety available in children.

Table 1
Review of DMARDs

Medicine	Indications	Summary of evidence	Dosage
Methotrexate (MTX)	Juvenile idiopathic arthritis (JIA), juvenile dermatomyositis/ polymyositis (JDM), uveitis, systemic lupus erythematosus (SLE), localized scleroderma and vasculitis	JIA Cochrane Review: 2 randomized controlled trials (RCTs) (165 patients) MTX effective on patient-centred disability, 3–23% greater with MTX than with placebo (*12*), a meta-analysis (*13*) a large RCT (*14*). JDM Use based on expert consensus (*15*) and 3 retrospective studies showing shorter discontinuation of steroids and reduced cumulative dose. Short- and long-term data suggest that MTX is a safe drug in the paediatric population (*16*, *17*).	Tablet 2.5 mg (0.0365/tab-cap to 0.1327/tab-cap)
Leflunomide	JIA	Several RCTs: leflunomide and MTX both produced clinical improvement; more patients on MTX met the primary end-point (ACR Pediatric 30 response) than on leflunomide (89% vs 68%, respectively) (*18*). Common adverse effects: headache, rash, and alopecia; liver abnormalities can occur. Teratogenic and requires liver function monitoring.	—
Sulfasalazine (SAS)	JIA	Two small RCTs showed superiority over placebo, but no significant difference with chloroquine. More adverse effects in the SAS group (*19*, *20*).	Tablet 500 mg (0.0865/tab-cap to 0.2349/tab-cap)

continues

Table 1 *continued*

Medicine	Indications	Summary of evidence	Dosage
Sulfasalazine (SAS)	JIA	A third trial showed no efficacy of SAS over placebo (n=33) (*21*). SAS does not have consistent efficacy across subtypes of JIA (poor tolerance). Adverse effects include rash, gastrointestinal symptoms and leucopenia, resulting in discontinuation in up to 30% of patients (*19*). Liver abnormalities and serious, even fatal, liver toxicity is associated with the DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms). Agranulocytosis has been reported in 1% of patients.	Tablet 500 mg (0.0865/tab-cap to 0.2349/tab-cap)
Cyclosporine (CyA)	JIA	Non-RCTs A prospective open trial over 10 years in 34 children with systemic onset JIA showed no effect on arthritis, and poor tolerance with 76% withdrawals (15/34 children for lack of efficacy and 9/34 for adverse effects) (*22*). Renal toxicity and hypertension are the most common adverse effects of CyA and main causes for withdrawal of therapy (*23*); other adverse effects include hypertrichosis, gingival hyperplasia, gastrointestinal (GI) disturbances, tremor, paresthesias, hepatic dysfunction and bone marrow suppression. Risk of secondary malignancies is increased at high doses. Nephrotoxicity is increased when combining CyA with other nephrotoxic medicines such as NSAIMS. CyA use requires monitoring of blood pressure, and renal function.	Tablet 25 mg (0.2860/tab-cap to 0.3576/tab-cap) Solution 100 mg/ml (1.1538/ml to 4.0789/ml)

continues

Table 1 *continued*

Medicine	Indications	Summary of evidence	Dosage
Azathioprine (AZA)	Refractory JIA, SLE	Refractory JIA – single RCT of AZA in 32 children with JIA failed to show efficacy over placebo (*24*). Observational studies suggest clinical and laboratory improvements (*25*) of paediatric SLE; and a small observational study suggested survival gains (*26*). Safety data: frequent GI symptoms in up to 12% of patients receiving AZA, less common pancreatitis, liver toxicity, interstitial pneumonitis, and serious dose-dependent adverse effects on bone marrow (genetically low thiopurine methyltransferase TMTP activity).	Tablet 50 mg (0.1379/tab to 0.1724 /tab)
Hydroxychloroquine (HCQ)	JIA	JIA 2 RCTs: (*27*, *28*) HCQ (6 mg/kg) vs penicillamine in 162 patients: no significant difference; and in 72 patients, HCQ was not more efficacious than gold or penicillamine. Rheumatoid arthritis (RA): a Cochrane Review comparing HCQ to placebo in adult patients with rheumatoid arthritis revealed an overall moderate effect and low toxicity profile (*29*).	Tablet 200 mg (0.1100 /tab-cap to 0.1986 /tab-cap)

Hydroxychloroquine

For hydroxychloroquine (HCQ), currently not in the EML, the Committee considered that there is evidence for efficacy and safety in adult SLE: a RCT (Canadian Hydroxychloroquine Study Group) showed that adult patients assigned to the placebo group had a significantly higher relative risk of flare and shorter time to flare compared to those patients who continued HCQ; and a recent systematic review of 95 articles (all ages) that concluded that there was evidence that antimalarials used in lupus prevent lupus flares and increase long-term survival of patients with SLE, and moderate evidence of protection against irreversible organ damage, thrombosis, and bone mass loss, with infrequent and reversible toxicity (*9*). The low cost of HCQ is an advantage for a systematic prescription in SLE patients.

The Committee also noted that the Childhood Arthritis and Rheumatology Research Alliance (CARRA) recommends hydroxychloroquine for milder cases of juvenile dermatomyositis and cases mainly characterized by rash (*10*). In children the recommended dose is 3–5 mg/kg per day with a maximum of 400 mg (as once or twice daily with food).

The Committee noted that HCQ is generally safe, including during pregnancy and breastfeeding. Common adverse effects include gastrointestinal (GI) and central nervous system (CNS) disturbances. The most serious irreversible adverse effect, however, is retinal (macular) toxicity, which can lead to blindness. The maximum safe daily dose in adults is 6.5 mg/kg, but is not defined in children (European Union, EU, product information). Detection of early retinal changes requires yearly monitoring and, if discovered, should lead to discontinuation of HCQ.

The Committee considered that there is evidence of effectiveness for hydroxychloroquine in SLE and recommended its inclusion in the EMLc Complementary List with availability of ophthalmologic monitoring as a condition for its use. A review in respect of adults would be prepared for the next meeting.

Leflunomide, sulfasalazine, azothiaprine, cyclosporine, mycophenolate

The Committee considered that although the review recommended the inclusion of leflunomide, it appears less effective than methotrexate with a similar safety profile and therefore did not recommend its inclusion in the Model List. Similarly, despite the recommendation made in the review, the Committee considered that the evidence supporting the use of sulfasalazine and azothiaprine in JIA was too limited and indicated poor tolerance and the need for regular monitoring to detect potentially serious adverse effects. The

Committee also considered that the evidence of efficacy for cyclosporin was insufficient to recommend inclusion.

Mycophenolate was not addressed in the application but commented upon by the second reviewer. The Committee noted that there is limited evidence in children indicating the possibility to reduce steroid doses (*11*) but no evidence of benefits over cyclophosphamide in adults with lupus nephritis. The Committee considered that there was insufficient evidence of effectiveness and safety to support inclusion in the EMLc.

Lastly, the Committee signalled the need for a review of the order of chloroquine versus hydroxychloroquine as a DMARD in adults.

Section 4: Antidotes and other substances used in poisonings

Section 4.2: Specific

Oral iron chelation therapy (review) – Children

In 2009, the Expert Committee requested a review of iron chelators for children. The current EMLc includes deferoxamine only, for parenteral use. Dr A Algren prepared the review for the Committee.

Expert reviews were provided by Dr Gregory L Kearns and Dr Lisa A Bero.

The Committee noted a recent review of iron chelators (*30*).

Acute iron intoxication can occur in both adults and children and can be fatal. Treatment includes supportive care, and parenteral deferoxamine. Chronic iron overload is due mainly to repeat transfusions, in patients with haemoglobinopathies. Other conditions requiring repeat transfusions include myelodysplastic syndromes, and (more rarely) haemochromatosis. Long-term consequences of chronic iron overload include multiple organ dysfunction (heart, liver, and endocrine), and/or failure, and death. Heart failure due to iron myocardiopathy is the main cause of death in thalassaemia patients.

The Committee reviewed the evidence available for acute iron poisoning. Two studies in volunteers showed that iron removal was possible with high doses of oral deferoxamine. The Committee noted that a recent placebo-controlled trial of deferasirox (20 mg/kg) showed iron elimination after a 5 mg/kg iron dose in volunteers (*31*).

A systematic review of observational and prospective studies suggests beneficial effects of deferoxamine on morbidity (notably cardiac disease and liver iron overload) and mortality, including with subcutaneous use (*32–37*). In sickle-cell disease, evidence is more limited but supports the use of deferoxamine. Deferoxamine has adverse effects on growth and maturation, auditory, and ophthalmic function. The Committee considered that the main limitation of deferoxamine was however the need for prolonged parenteral administration,

REPORT TRUNCATED

The Selection and Use of Essential Medicines

This report presents the recommendations of the WHO Expert Committee responsible for updating the WHO Model Lists of Essential Medicines. It contains a summary of the Committee's considerations and justifications for additions and changes to the Model Lists, including its recommendations. Annexes to the main report include the revised version of the WHO Model List of Essential Medicines (17th edition) and the WHO Model List of Essential Medicines for Children (3rd edition). In addition there is a list of all the items on the Model Lists sorted according to their Anatomical Therapeutic Chemical (ATC) classification codes.

An additional annex covers the Report of a Supplementary Meeting of the Expert Committee on the Selection and Use of Essential Medicines which took place in Geneva in January 2010 to consider treatment of the pandemic influenza virus.

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