make medicines child size

Report of the Third Partners' Meeting on Better Medicines for Children

Geneva, Switzerland
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Executive summary

The Better Medicines for Children project aims to promote better use of medicines in children, promote access to medicines for children, fill knowledge gaps about priority medicines for children and promote research and development of essential medicines for children. The project is funded by the Bill and Melinda Gates Foundation and is the third year of implementation.

A partners meeting was held to share information on progress related to the Better Medicines for Children project; to consider the challenges related to improving access to and use of medicines for children; to collaborate on approaches to meeting the challenges and to define priority areas for action to complete the objectives set out in resolution WHA60.20 on Better Medicines for Children. The meeting was attended by WHO staff from the Medicines, Access and Rational Use team, country implementation teams and experts, researchers and representatives from organizations having an interest in Better Medicines for Children.

Progress has been made by WHO on a number of areas such as publication of the third edition of the *WHO Essential Medicines List for Children* and the *Priority medicines for mothers and children*. The Paediatric medicines Regulators Network continues to strengthen its activities and recently contributed to the development of the *Guidance on assessing clinical trials in children*. Several documents were presented to the 54th Expert Committee on Pharmaceutical Specifications- *Development of paediatric medicines: points to consider in formulation* which was adopted by the Committee and *A review on extemporaneous, or compounded, formulations* which will be developed further. Progress has been made in Ghana and India, in completing baseline surveys and in adapting national Essential Medicines Lists to include medicines for children. A number of global initiatives contributing to Better Medicines for Children are under way.

Work is still needed in order to develop effective interventions to improve access to and use of medicines in children. Further research and development for appropriate formulations is required particularly on research for appropriate formulations for paediatric tuberculosis treatment and treatment of HIV in young infants. Actions are needed to expedite market access while assuring quality through the regulatory process. Guidance and tools are needed to improve selection and procurement and supply chain management. Funding, advocacy and partnerships with key stakeholders is needed to carry this work forward.

As a way to address several priority areas which were discussed during the meeting, working groups were formed to explore and address: 1. roles and responsibilities for advancing work on paediatric tuberculosis formulations; 2. communication approaches for stimulating demand for appropriate medicines for children; 3. identifying key players who

could create a demand for children's medicines; 4. proposal for development of regulatory pathways for 'common' quality assurance in regions; and 5. facilitating national Essential Medicines Lists to include a focus on children's medicines.

Introduction

Overview

The work of many governments, United Nations organizations, universities, nongovernmental organizations, the private sector and funding agencies led to the passing of the World Health Assembly resolution on better medicines for children (WHA60.20[1]) in May 2007. Following the resolution and with the support of a grant from the Bill and Melinda Gates Foundation, the World Health Organization, Department of Essential Medicines and Pharmaceutical Policies in collaboration with many partners has made great progress on supporting country and global efforts to reduce child mortality through better access to medicines that are designed to meet the needs of children. WHO is committed to improving access to and use of medicines for children, and a new UN Commission on overlooked commodities will provide a helpful context for further work, as will the UN Secretary General's interest in mother and child health.

This report outlines the highlights of the Third Partners Meeting on Better Medicines for Children and the discussion on the way forward. Presentations are available upon request.

Meeting objectives

To share information on progress related to the Better Medicines for Children project

The Third Partners' Meeting on Better Medicines for Children took place at the end of the 3rd year of the Gates funded project. The meeting provided an opportunity to share information on the progress made by WHO, in countries and through numerous global initiatives over the past year.

To consider the challenges related to improving access to and use of medicines for children and to collaborate on approaches to meeting the challenges

The meeting was attended by approximately 50 representatives from various organizations working towards improved health outcomes for children. The commitment to continued partnership and the strength of the partners' collaborations was recognized as a key factor in the progress made on better medicines for children.

> *'The challenges are vast but they are not insurmountable. Through partnership and continued effort we can overcome many of the barriers that prevent the right medicines from reaching the children who need them.'*
>
> Carissa F. Etienne in her welcoming remarks

1 www.who.int/childmedicines/publications/en/

To define priority areas for action
A report on progress on the Better Medicines for Children initiative is due at the World Health Assembly in 2012. Participants at the meeting made suggestions on key strategies to improve availability in countries.

Progress made

WHO

WHO, as the Secretariat of the better medicines for children project, works on the development of normative guidance, identification of gaps in knowledge, regulatory initiatives and country support. Work occurs across all WHO programmes to ensure that safe and effective medicines are made available for children. WHO also promotes norms and standards for the quality and safety of children's medicines and to build regulatory capacity. It supplies treatment guidelines and information on medicines, and encourages adequate financing for medicines for children.

During the last year notable progress has been made on the WHA resolution on better medicines for children directives, namely:

1) The development of global norms and standards

- The third edition of the *WHO Model List of Essential Medicines for Children*[1] was published following the Expert Committee Meeting on the Selection and Use of Medicines that met in March 2011. The list is a valuable tool for countries in developing their own national Essential Medicines Lists.
- The list of Priority Medicines for Children[2] was launched this year highlighting those medicines with the greatest impact on child mortality.

2) Working with all WHO programs to ensure that they contribute to making safe and effective medicines available

- Examples of departmental collaborations in WHO are with Essential Medicines and Pharmaceutical Policies, Stop TB, Global Drug Facility, HIV, Roll Back Malaria and Child and Adolescent Health.

1 www.who.int/medicines/essentialmedicines

2 www.who.int/childmedicines/prioritymedicines

3) Promotion of norms and standards for quality and safety of children' medicines and regulatory capacity

- A new guidance document on assessing clinical trials in children[1] has been published to help clinical trial assessors and their agencies improve their capacity to assess trials in paediatric populations.
- The Paediatric medicines Regulators Network (PmRN)[2] comprising 30 members was established as a forum to discuss and raise awareness of paediatric medicines regulatory issues. Members met in Dar es Salaam in October 2011 where training on the use of the above guideline was undertaken.
- The document: Development of paediatric medicines: points to consider in formulation was adopted by the 54th Expert Committee on Pharmaceutical Specifications[3]. The document informs regulatory authorities and manufacturers about specific challenges in pharmaceutical development of paediatric medicines, through reference to relevant literature.
- Collaborations with the European Medicines Agency will produce improved paediatric dosing guidelines.

4) To make available treatment guidelines and medicines information

- *WHO recommendations on the management of diarrhoea and pneumonia in HIV-infected infants and children* has been published[4].
- The new edition of the Pocketbook for Hospital Care for Children[5] will be launched shortly.
- *WHO Guidelines on Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses* is in press.
- The results of a review of priority medicines for children on national Essential Medicines Lists will be published in a journal article. Although national Essential Medicines Lists are a key tool for introducing medicines, the study shows that priority medicines for children are often not listed.

1 www.who.int/childmedicines/CTguidance

2 www.who.int/childmedicines/paediatric_regulators

3 www.who.int/medicines/services/expertcommittees/pharmprep_meet

4 www.who.int/child_adolescent_health/documents/9789241548083

5 www.who.int/child_adolescent_health/document/9241546700

- A study of current administration practices and preferred formulations of children's medicines in Tanzania was carried out by Dartmouth Medical School. The study showed an overwhelming preference for sweet tasting medicines. It showed that most children are being given pills in whole or crushed form despite the negative impact on adherence. This study, which is also proceeding in Ghana, will be published.
- A practical solution to the problem of weight estimation where there are no calibrated scales, called TAPE (Taking the Guesswork out of Pediatric Weight Estimation) was validated in India and Mali. There are plans to carry out validation in China as well. The method has thus far proved reliable in all populations studied and has shown to be advantageous over existing methods.
- A review on extemporaneous, or compounded, formulations was commissioned to review existing guidance on how medicines should be administered to children where no paediatric products are available, and to provide instruction on making compounded preparations safely. The draft guidance[1] was presented to the 54th Expert Committee on Pharmaceutical Specifications. There were concerns that adoption of the recommendations would divert efforts aimed at the development of age-appropriate dosage forms for children and that conflicting signals would be given that could seem to endorse the use of adult dosage forms in children. The Committee advised that the document should be further developed by WHO, FIP and GRIP to help those practitioners needing to make compounded products in the case that all steps had been taken to avoid extemporaneous compounding.

5) Collaborating to encourage fair trade and adequate financing for medicines for children

- An informal working group on market shaping for priority medicines for children has been established which will contribute to the new UN Commission on overlooked commodities, that will begin work in 2012.
- Pricing guidelines for paediatric products are under development.

1 Reference to the document commissioned by Sue Hill and drafted by Tony Nunn. Provision by health-care professionals of patient-specific preparations for children that are not available as authorized products-points to consider. Working document QAS/11.399/Rev.1

Countries

Progress made on the better medicines for children project in Ghana and India was presented. Summaries of the work carried out thus far are as follows:

Ghana

The better medicines for children project was launched in Ghana in April 2010. Through the project, access to essential medicines for children is being promoted; advocacy with policy makers is being carried out for inclusion of medicines for children in Essential Medicines Lists, treatment guidelines, National Health Insurance and procurement schemes; work with drug regulatory authorities to expedite regulatory actions on specific medicines for children is ongoing; and measures to monitor availability, prices and quality of medicines for children are being carried out.

The following reports have been published on the Ghana Better Medicines for Children website[1] and on the WHO web site[2]:

- Desk review of existing literature on medicines for children in Ghana
- Price , availability and affordability of medicines for children
- Supply chain assessment of medicines for children
- Assessment of the quality of care for children in selected hospitals
- Assessment of local manufacturing capacity for child specific dosage forms
- Peer review workshops for Drugs and Therapeutics Committees

The following studies are under way:

- Neonatal quality of care. This initiative will horizontally integrate WHO guidelines with better supply of priority medicines, on-site clinical education and continuing support to improve the quality of care of neonates at the district hospital level in Ghana, focusing on neonatal asphyxia and sepsis.
- Prescription audit. The audit will compare prescribing practices for children to standard treatment guidelines for specific diseases and conditions. It will also assess stock levels and propose strategies to avoid stock-outs.

1 ghndp.org/childmedicines

2 www.who.int-childmedicines/countries

Results of efforts thus far:

- Active engagement with the private sector has led to development of dispersible, taste-masked zinc sulphate tablets in country.
- Adaptation of the Pocketbook of Hospital Care for Children is in process.
- Capacity building has taken place for the national Essential Medicines List Selection Committee and an Evidence Profiles Development Group. Trainings included: 1. Pharmacoeconomics course, 2. training in understanding evidence synthesis, 3. support for production of evidence summaries, 4. ML/STG expert group meeting. Work resulted in proposals for additions of artesunate and zinc to the Essential medicines List and National health Insurance List.
- Participation in research studies has led to increased research capacity.
- The role of Drugs and Therapeutic Committees as agents for rational use of medicines at the facility level has been strengthened.
- One local company is applying for prequalification for zinc production.

India

The Better Medicines for Children project in India aims to improve the availability of essential medicines for children by developing and implementing an Essential Medicines List for children (EMLc) in two states: Chhattisgarh and Orissa. In addition an EMLc for children with 134 medicines listed has been prepared by the Indian Academy of Paediatrics and published on their website. The EMLc is ready in Orissa but its application in procurement is blocked by a legal battle between local manufacturers and the State of Orissa. Money is available for procurement of medicines for children, but procurement officers are unable to spend it.

Pricing and availability surveys were carried out in both states. Results show that public sector availability of essential medicines was poor and higher in the private sector. Reports will be available shortly[1].

Other work:

- Validation of an alternative method for weight estimation (see TAPE below) was carried out in two sites
- A review of paediatric clinical trials registered in the Clinical Trial Registry India was carried out.

1 www.who.int/childmedicines/countries

- Initiatives were taken to include paediatric clinical pharmacology in the medical curriculum.
- 400 medical officers are being trained in Chattisgargh.
- Training of trainers and training of pharmacists on supply chain management in Orissa is planned.

Global initiatives

A number of global initiatives are under way which contribute to Better Medicines for Children. Progress on the following initiatives was shared:

- Global Research in Paediatrics[1] (GRIP) is a consortium funded by the European Commission to facilitate the development and to promote the availability of medicines for children by coordinating work, thereby reducing the fragmentation of ongoing efforts in relevant fields of research. GRIP also aims to create consensus on international standards, methodologies and tools for paediatric research. Work is focused on:
  - The development of a Paediatric Clinical Pharmacology Training Programme which aims to build expert capacity for the development, study and regulatory assessment of paediatric medicines.
  - Training for health-care personnel (physicians, nurses and pharmacists involved in paediatric clinical trials).
  - Filling important gaps in paediatric medicines research by validation and harmonization of research tools specific to paediatrics
  - Sharing of strategies and plans.
- The Drugs for Neglected Diseases Initiative[2] (DNDi) works with public and private institutions and philanthropic entities to advance drug research and development. The current disease portfolio of the Drugs for Neglected Diseases Initiative (DNDi) includes Leishmaniasis, Human African Trypanosomiasis, Chagas disease, Helminths and more recently, paediatric HIV (see discussion on HIV below). All diseases of the portfolio significantly affect young children. As new chemical entities are entering clinical phase, it will be crucial to identify the most appropriate route for their development in children.

1 http://grip-network.org

2 www.dndi.org

- The International Pharmaceutical Federation (FIP) presented the *FIP reference paper on the effective utilization of pharmacists in improving maternal, newborn and child health (MNCH)*[1]. The paper illustrates the different ways that pharmacists are currently improving maternal and child health using the Joint FIP/WHO Guidelines on Good Pharmacy Practice framework[2].
- The Ecumenical Pharmaceutical Network[3] (EPN) presented data from a multi-country study on availability and pricing of selected medicines for children in Faith Based Organization/ Drug Supply Organizations. EPN is celebrating 30 years since its inception.
- The HAART for Children Campaign[4] by Caritas calls for governments and pharmaceutical companies to respond to the needs of children living with HIV and HIV-TB co-infection. An example of the work in Australia was presented whereby awareness of HIV was raised and manufacturers were targeted through a postcard and email campaign.
- A study carried out by the Medicines for Malaria Venture[5] showed how to facilitate the uptake of solid child-friendly ACTs in francophone Africa (see discussion on malaria treatment below).

Panel discussions

Market shaping panel

Francisco Blanco (UNICEF), Alexis Heaton (JSI), Lisa Hedman (WHO), Saul Morris (Gates Foundation), Nine Steensma(CHAI), Renee van de Weert (UNICEF)

The panel shared information on a new United Nations Commission that is being set up in response to the need for improved access to medicines for children in countries. UNICEF and UNFPA will act as the Secretariat for the Commission and Heads of State and high level representatives from various organizations will be involved. Working groups will be assigned specific tasks by the Secretariat to be completed in time for the WHO health Assembly in May.

1 http://www.fip.org/www/uploads/database_file.php?id=325&table_id=

2 World Health Organization and International Pharmaceutical Federation. Joint FIP/WHO guidelines on good pharmacy practice: standards for quality of pharmacy services in Forty-fifth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO technical report series No. 961). Geneva: World Health Organization; 2011

3 www.epnetwork.org

4 www.caritas.org/activities/hiv_aids/HighlightsOfHAART.html

5 www.mmv.org

The panel also shared information on the progress made on market shaping by an informal working group represented by the panel. The group has used the Ishikawa model to look at a subset of medicines on the priority list to better understand why the ideal products are not available and to identify actions needed. This work will feed into the UN Commission's work.

There is no uniform answer to access and some products require more work than others. Some require product development, defined regulatory pathways, quality improvements or financing to improve availability. Others require more simple solutions for packaging or labeling. Small markets or markets that have an uncertain size are unattractive to manufacturers.

Despite progress with regulatory harmonization initiatives across Africa, fragmented procedures create barriers for manufacturers particularly for 'overlooked' commodities. Regulatory pathways differ and some pathways are not clear. For example, zinc could be considered a pharmaceutical product or a nutritional substitute. Chlorhexidine could be considered as a pharmaceutical or a disinfectant.

The question of how to get regulatory authorities to expedite approvals without compromising on quality was discussed. Prequalification may not be the answer to quality assurance for all priority medicines. An Expression of Interest for zinc has been presented by the prequalification programme since 2009. Despite very clear requirements, there has been very limited interest from manufactures. Three products have been submitted and under evaluation[1]. The reasons for the limited interest need to be understood.

Some options to reducing the regulatory burden on manufacturers were discussed that could be explored further, including:

- A federated option whereby regulatory authorities in a region agree to recognize a common approach. Financial or other inducements could be used to encourage participation.
- A centralized option where all questions from each regulatory authority would be received in a clearing house to streamline the questions and eliminate repetitions.
- Training to focus on the importance of the question. This would eliminate nonessential questions on the dossier. This method has been successful with UK ethics commission.

1 http://apps.who.int/prequal/

Regulatory panel

Dr Samvel Azatyan, Dr Hans Stötter and Dr Chkukilizo

The panel presented several initiatives to improve harmonization, capacity building and collaboration. There are 5 countries involved in a harmonization project in East Africa. One set of documentation is required for registration and the assessment is carried out jointly. Registration times for this approach are shortened to weeks instead of months.

Harmonization is easier when there is collaboration among countries, facilitated by working in a common language, and when capacity is similar.

The Paediatric medicines Regulatory Network (PmRN) offers opportunities for members to learn from each other and recently carried out training in Tanzania. The training module will be made available on the WHO website[1]. SwissMedic has a Memorandum of Understanding with several countries to exchange assessments so that has agencies do not have to repeat. This may be a model for capacity building. The European Paediatric Regulation requires applicants to submit an agreed paediatric investigation plan/waiver for the marketing authorisation of any new medicinal product (even if only intended for adults). For already authorized patent-protected medicinal products this applies for any new indication, pharmaceutical form or route of administration. Scientific advice for medicinal products for paediatric use is offered free of charge.

The challenge is to find the balance between expediting market access and assuring quality through the regulatory process. A risk based approach is needed to assess the consequence of regulatory decisions.

It was suggested that the PmRN could be a useful mechanism for communicating new information to countries.

The question on what type of regulatory approach will work for 'overlooked' medicines was deferred to a working group session for Day 2 (see below).

1 www.who.int/childmedicines

Action areas

The following areas were identified as areas where work is still needed:

Selection of medicines in countries

Guidance and tools are needed for developing and updating national Essential Medicines Lists. Countries should not be expected to start from scratch. Raising awareness on what is available on the WHO model list and making that information more accessible could help. Products should be available before selection takes place.

Regulation

The European Medicines Agency has published a draft Guideline on Pharmaceutical Development of Medicines for Paediatric Use[1] for public comment. Participants reported that they and others had found this document too prescriptive and agreed that greater flexibility was required. The deadline for comment is 31 December 2011. It was agreed that a statement would be written and shared with all participants to facilitate comment by the various organizations. The following comments were thus developed by GRIP participants:

1 www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500107908

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Comments on EMA draft guideline: "Guideline on Pharmaceutical Development of Medicines for Paediatric Use"

The draft guideline is problematic because it is often prescriptive in the absence of evidence and presents "points to consider" as specific regulatory guidance. If these "points to consider" become fixed guidance there will be unnecessary limits put on the development of medicines for children.

In the absence of evidence about many key points a better way forward would be to develop an updated "points to consider" document." reflecting the following:

1. There is a need to base recommendations about dosage forms on clinical requirements and justification of the dosage form.

- The methods of administration (lines 240 – 246) need to be evidence based, or not included as specific regulatory guidance.
- Guidance should say that tablet size should justified and if there is not solid data, research should be proposed.
- Only make statements about tablet sizes if there is an evidence-base e.g. lines 247 – 253.
- Mini-tablets could be used in many age groups. As drafted the guideline could stifle the development of mini-tablets
- Justify volumes for dispersible dosage forms 282 – 285 (or rephrase to meet clinical reality).
- Justify recommendations for capsules 309 – 312 (or rephrase to meet clinical reality).

2. The guideline appears to cover two different scenarios: a. formulation development de novo and b. using medicines already on the market.

- The scenarios need to be considered separately, possibly in separate guidelines.
- Capsules (lines 300 – 302) may only be suitable for existing medicines.

3. Need to match guidelines to appropriate specifications: guidelines cover scenarios that are not covered by relevant quality requirements.

- Line 268 assumes that Eu Pharm or other documents include a specification for content uniformity as well as weight uniformity.
- Droppers (line 351) are not in Eu Pharm or any other specifications.

4. Need to consider a guideline for making age-appropriate formulations of existing medicines used as comparators in trials.

5. Is the time limit proposed for the reevaluation of existing medicines realistic? Will it lead to unintended consequences if the sanction for failing to comply is withdrawal of marketing authorizations?

6. If manipulations will be needed due to special situations, the manipulations should be validated (209 – 214).

The Pan African Clinical Trials Registry (PACTR) has recently launched a new web site[1]. This is an open-access platform where clinical trials can be registered free of charge. The PACTR aims to increase clinical trial registration in Africa by developing awareness of the need to register trials and supporting trials during registration. PACTR provides a searchable, electronic database of planned trials and trials currently in progress; its dissemination among stakeholders would be beneficial.

Estimation of body weight

Further studies of the TAPE method are planned that will assess its acceptability to health care workers and parents, who are more used to weighing scales - though these are often not calibrated. Emergency and community health care workers will take part in the studies, and some sites where scales are not available are to be included. The results of trials so far show a higher degree of accuracy than with other measuring devices. Lightweight tapes could be supplied at low cost, and could even be folded and inserted in packages of medicines by manufacturers.

Compounding/extemporaneous dosing

This is a practice which will continue to occur when appropriate medicines for children are not available. A strong message needs to go out that compounding should not be done if an appropriate formulation is available. The possibility of compounding must not be used an excuse to avoid developing age-appropriate formulations.

HIV

Issues

- More dosage forms and strengths exist today for the treatment of paediatric HIV than are needed, fragmenting a small market.
- Current treatment options for HIV-infected infants and young children are very limited as little investment has been made by the industry to develop child-appropriate formulations.
- Ideal product formulations for young infants are not available. The one that is most needed is a replacement of the current lopinavir/ritonavir solution which tastes terrible, requires, refrigeration, and contains 42% of alcohol and 15% propylene glycol.
- HIV is a progressive and painful disease, requiring pain management.

1 www.pactr.org

- Country governments are failing to put resources behind financing antiretrovirals for children. 75% of children are supported by UNITAID funding. There is a concern from many about the future of paediatric treatment scale up especially considering the exit of UNITAID from its paediatric program and the funding crisis of the Global Fund.
- Early infant diagnosis is critical to detect and increase the number of younger children who need treatment. Development of point-of-care early infant diagnosis is important to achieve this.

Way forward

- Development of a shorter, selective list of paediatric formulations is under way in order to focus on what is most urgently needed. The 'optimal' list will be published on the web to invite comment.
- "A working group (Supply Consortium) has been organized with the objective of coordinating pediatric antiretroviral procurement, while addressing related issues such as optimization of pediatric formulations/treatments. Under coordination from the Global Fund, it will be operationalized during 2012 towards full implementation in 2013. Consultations with technical partners, stakeholders - and their procurement agents, have already taken place (UNITAID, CHAI, WHO, PEPFAR and Global Fund, UNICEF) and others ongoing (MSF, OECS).. This could be a model for 'overlooked' commodities.
- Advocacy with industry to expedite better paediatric antiretrovirals is ongoing
- DNDi is working on the development of an improved Protease Inhibitor fixed dose combination for children under 3 years of age to replace the currently used lopinavir/ritonavir liquid formulation i.e a safe, easy to administer, well-tolerated and palatable, heat-stable, readily dispersible formulation. In parallel DNDi is also developing a boosting agent that can be used in HIV-TB co-infected infants to overcome the negative drug-drug interaction between Protease Inhibitors and rifampicin (CYP3A4 induction).
- The medicines patent pool may help speed up the development of paediatric HIV medicines by removing the intellectual property barriers.

TB

Issues

- Rapid Advice1 was published in 2010, but the corresponding medicines remain unavailable on the market. Formulation of a new fixed-dose combination matching the new dosing is still an issue.
- Misperception on finality of the treatment guidelines.(Can you explain?)
- Disease burden for paediatric tuberculosis is uncertain and compromised by lack of child-specific diagnostic tools. A point of care diagnostic tool is needed, but no one is investing.
- Solving the regulatory issues and increased advocacy are critical.
- It is not clear who is leading the work on TB research for children – this must be resolved

Way forward

- Important to have a clear message on whether or not PK studies are needed and what regulatory pathways are needed.
- A working group will discuss roles and responsibilities (see below).

Malaria

Issues

- Emergence of resistance is accelerating yet many countries are still allowing artesunate and/or amodiaquine monotherapies.
- Appropriate products are available, specifically- solid child-friendly quality assured ACT formulations. However, more work needs to be done to facilitate their adoption.
- Health professionals are not sufficiently aware of the recommended formulations.
- Solid child-friendly formulations are accepted by those consumers that have had adequate training.
- More artemisinin-combination therapies (ACTs) need to be available.
- There is currently only one manufacturer of the artesunate + amodiaquine fixed dose combination product that has WHO prequalification. Four artemether and lumefantrine products now have prequalification including however, only one dispersible formulation. Three generics of artemether and lumefantrine dispersible are just reaching the market, none of which are pre-qualified.

1 Rapid Advice Treatment of Tuberculosis in Children. Geneva, World Health Organization 2010

Way forward

- Solid pediatric ACT formulations should be listed on national Essential Medicines Lists and in national Standard Treatment Guidelines in accordance with national policies.
- Procurement needs to be aligned with the Essential Medicines List nationally.
- Interventions are necessary to influence manufacturers to stop supplying and countries to stop importing monotherapies. Regulatory authorities need to be strengthened so that they have enforcement power. Donors should support the supply and use of appropriate products.
- UNICEF and Global Malaria Programme have an advocacy programme whereby companies affirm that they will not market monotherapies: this could be more widely stressed.
- The supply chain needs strengthening and free antimalarials sometimes constitute a supply barrier in countries where the system functions solely on cost recovery.
- Supply chains are still weak and need to be strengthened.
- The need for collection and dissemination of evidence for use of solid pediatric ACT formulations at international, regional and national levels requires attention.
- Training at the user level is important as this concept of solid pediatric tablet is new.

Working groups

As a way to address several priority areas which were discussed during the meeting, working groups were formed to explore and address: 1. Roles and responsibilities for advancing work on paediatric TB formulations; 2. Communication approaches for stimulating demand for appropriate medicines for children through country level activities; 3. Identifying key players who could create a demand for children's medicines; 4. Proposal for development of regulatory pathways for 'common' quality assurance in regions (trading blocs); and 5. Facilitating national Essential Medicines Lists to include a focus on children's medicines.

1. Roles and responsibilities for advancing work on paediatric TB formulations

Issue

The correct fixed dose Paediatric TB formulations are unavailable.

Recommendation of the working group

The lead role needs to be taken by Stop TB and/or the WHO Department of Essential Medicines, provided additional staff is recruited/seconded. Contracting out the organization of this work could be done by – for example - MSF or DNDi. The first task would be to write a justification and proposal to UNITAID and/or a foundation that might consider funding the costs of this work. andWHO should be centrally involve.

2. Communication approaches for stimulating demand for appropriate medicines for children through country level activities

Issue

There is a need is to increase the awareness of the availability and benefits of child specific products.

Recommendation of the working group

A starting point would be additional communication from WHO/Geneva or WHO Regional Offices to countries regarding "optimal products" for children, including a list of key products and the benefits of using, purchasing, and prescribing medicines for children. This information could flow from WHO country offices to governments and from there to country programs, procurement units, and provider networks.

Additional efforts could involve

- Working with countries to obtain realistic demand estimates for pediatric products to aggregate and share with manufacturers. Often suppliers do not have enough information to accurately assess the market opportunity to manufacture or develop pediatric products because adult formulations are being used or manipulated. Countries could forecast what % of current demand could be substituted with a pediatric product and what new demand might be met if a pediatric-specific product was available. This information would then have to be organized by an organization and shared with potential suppliers. This requires a realistic demand estimate, based on estimates of health care seeking behavior, not a morbidity-only forecast as that over-estimates potential demand and will not be credible with suppliers. Demand estimates from specific countries with likely funding sources can also help suppliers target their regulatory efforts.
- If demand is insufficient to create incentives for production and development, aggregated demand and articulation of clear need may be used to discuss with international financing bodies and suppliers what incentives, subsidies, or public private partnership would be necessary to overcome market barriers.
- Communicating with country programs and drug therapeutic committees (DTCs)
- Recommendations to update Standard treatment guidelines to specifically reference pediatric products (dispersible tablets in age-appropriate strengths).

- Working with procurement units to ensure that they have the correct pediatric product specifications (dispersible tablets in age- appropriate strengths in line with national treatment guidelines) and are including these products in quantification and procurement efforts if they are already commercially available; this might include communication about cost advantages if dispersible tablets are to be purchased in place of syrups and information about improved efficacy achieved through optimal products and the indirect cost of under/over dosing of manipulating adult products for children to counter any costs concerns related to paediatric specific products.
- Communication options to increase demand are greater with over the counter products as suppliers can advertise broadly and maximize reach, which in turn, increases competition. For products where this is appropriate, communicate advantages of over the counter status and increased delivery opportunities.
- For both over the counter products and prescription products, communicate advantages of pediatric products to professional networks to promote adoption, procurement and prescribing. Potential groups to target include pharmacist networks, paediatric groups, nurses, and where applicable, insurance organizations.

3. Key players for creating demand for medicines for children

Issue

Which stakeholders can best influence demand for medicines for children?

Recommendation of the working group

Defining demand is a complex and context dependent. We suggest that a working group develops a "Points to Consider" document about defining demand.

The working group should consider:

- Pooling existing knowledge such as case studies of successful and unsuccessful attempts to create demand and behaviour change techniques.
- A framework for a landscape analysis of medicines use (including existing players, supply chains, and margins).
- Engagement with industry to learn from them about creating demand and harnessing public-private partnerships to create a demand.

4. Proposal for development of regulatory pathways for 'common' quality assurance in regional blocks

Issue

Registration requirements differ from country to country, creating barriers for submission. The prequalification program has limited facilities and is not intended to play a "supranational" role in regulation.

Recommendation of the working group

The Pediatric medicines Regulators Network could facilitate the stepwise harmonisation of regulatory requirements and approvals, based on the International Conference on Harmonisation (ICH) Common Technical Dossier (CTD). A starting point would be within Regional Blocks such as the East African Community, Association of Southeast Asian Nations (ASEAN), Economic Community of West Africa States (ECOWAS) and South American economic blocks. Second would be to harmonise between blocks.

The areas of harmonisation will be: common assessment templates, inspection procedures and auditing; and conducting joint assessments, inspections and auditing and using the report to make in-country decisions. This will reduce the burden of multiple dossiers, duplication of efforts, and help to build capacity and trust among different regulators.

This harmonization will be important for exchange of approved medicines and for import of medicinal products from foreign production sites. Therefore it will be key to availability of medicines on the essential medicines list including medicines for children.

5. Facilitating country Essential Medicines Lists with a focus on children's medicines.

Issue

Evidence based selection of medicines is an important process for the rational use of medicines. Facilitation of the process for creating or modifying a national Essential Medicine List is needed.

Recommendations of the working group

As a first step, convince decision makers and policy makers to implement the Essential Medicines List. They need to see and understand the evidence. There is a real need to improve how this is communicated.

Guidance on and tools for developing national Essential Medicines Lists are needed and should include how to assess applicability, feasibility and cost. Countries should have access to easily accessible evidence summaries so that work does not need to be repeated. Health Technology Assessments could be shared between countries.

Agenda

Day 1

Chair: Mrs Philippa Saunders (Oxfam)

WHO Better Medicines for Children project		
09.00 - 09.15	Introduction and welcoming remarks	Dr Carissa Etienne Assistant Director-General, HSS
09.15 - 9.30	Better Medicines for Children: lessons learned and the way forward	Dr Clive Ondari (EMP/MAR)
9.30 - 9.45	Priority medicines on country essential medicines lists	Dr Lisa Bero (University of California San Francisco)
9.45 - 10.00	Discussion	
Technical updates		
10.00 - 10.20	Current Administration Practices and Preferred Formulations of Children's Medicines in Tanzania	Dr Lisa Adams (Dartmouth College)
10.20 - 10.40	Break	
10.40 - 11.00	Weight estimation study	Dr Susan Abdel-Rahman (Children's Mercy Hospitals and Clinics)
11.00 - 11:20	Extemporaneous formulations	Dr Mark Turner on behalf of Dr Tony Nunn (University of Liverpool and UK NIHR Medicines for Children Research Network)
11.20 - 11.40	Update on the outcome of Expert Committee regarding the development of paediatric guidelines	Ms Xiaoqiong Zheng, QSM
Partner updates		
11.40 - 12.00	DNDi	Dr Nathalie Strub-Wourgaft and Ms Janice Lee (Drugs for Neglected Diseases Initiative)
12.00 - 12.20	Future of paed ARV formulation	Dr Sahffiq Essajee HIV Department
12.20 - 12.40	Global Research in Paediatrics (GRIP): Overview of activities	Dr Mark Turner (University of Liverpool and UK NIHR Medicines for Children Research Network)
12.40 - 13.00	Global Research in Paediatrics (GRIP): Training in clinical paediatric pharmacology	Dr Kalle Hoppu (IUPHAR and IPA)

Day 1 continued

13.00 - 13.45	Lunch	
13.45 - 14.05	FIP reference paper on the effective utilization of pharmacists in improving maternal, newborn and child health (MNCH)	Mr Luc Besançon International Pharmaceutical Federation
14.05 - 15.05	Panel discussion and plenary activity: Market shaping	Moderator: Ms Lisa Hedman Panel: Dr Saul Morris, Ms Alexis Heaton, Ms Nine Steensma, Dr Renee Van Weerdt, Mr Francisco Blanco
15.05 - 15.25	Break	
15.25 - 16.15	Panel discussion: Regulatory initiatives to promote access to paediatric formulations	Moderator: Dr Samuel Azatyan (EMP/QSM) Panel: Dr Hans Stötter (Swissmedic), Dr NB Chukilizo, TFDA
16.15 - 16.45	Wrap up day 1	Dr Clive Ondari (EMP/MAR)

Day 2

Chair: Philippa Saunders

WHO Better Medicines for Children Country work		
09.00 - 09.30	Progress on better medicines for children in India	Dr Kris Weerasuriya (EMP/MAR) on behalf of Dr K. Holloway, RA/SEARO and Dr G. Batmanabane, SEARO
09.30 - 10.00	Progress on better medicines for children in Ghana	Mrs Martha Gyansa-Lutterodt (Ministry of Health Ghana)
10.00 - 10.20	Producing evidence summaries to facilitate evidence-based medicine selection in Ghana'	Dr David Sinclair (Liverpool School of Tropical Medicine)
10.20 - 10.40	Neonatal quality improvement	Dr Fizan Abdulla (Johns Hopkins University)
10.40 - 11.00	Discussion	
11.00 - 11.15	Break	
Programme updates		
11.15 - 11.35	Portfolio of faith based organizations-drug supply organizations with focus on childrens' medicine	Mr Albert Petersen (Ecumenical Pharmaceutical Network)
11.35 - 11.55	Management of pain in children	Dr Willem Scholten (EMP/MAR)
Paediatric HIV, TB, Malaria and other specific disease areas		
11.55 - 12.10	HAART for children	Msgr Robert J Vitillo (Caritas Internationalis)
12.10 - 12.25	Paediatric HIV- next steps	All participants
12.25 - 13.15	Lunch	
13.15 - 13.30	How can we facilitate access to solid paediatric ACT formulations in francophone Africa?	Dr Florence Camus-Bablon (Medicines for Malaria Venture)
13.30 - 13.45	Paediatric ACT- next steps	All participants
13.45 - 14.00	Overview of Paediatric TB	Dr Malgosia Grzemska (Stop TB Dept)
14.00 - 14.15	Paediatric tuberculosis - next steps	All participants
14.15 - 14.45	Other disease areas	All participants
14.45 - 15.00	Coffee	
Action areas		
15.00 - 16.00	Working groups	All participants
16.00 - 16.30	Reports from group work	
16.30 - 16.45	Wrap up & identification of action areas	Dr Clive Ondari (EMP/MAR)

List of participants

PARTNER	REPRESENTATIVE
BILL & MELINDA GATES FOUNDATION 1551 Eastlake Ave. E Seattle, WA 98102, USA	**Dr Saul S. Morris** Senior Programme Officer, Child Health Family Health Division E-mail: Saul.Morris@gatesfoundation.org
CARITAS INTERNATIONALIS 1, rue de Varembé 1202 Geneva, Switzerland	**Msgr Robert J Vitillo** Head of Delegation E-mail: bobvitillo@cs.com
The CHILDREN'S INVESTMENT FUND FOUNDATION (UK) 7 Clifford Street, London W1S 2FT UNITED KINGDOM	**Ms Suzanne Fournier** Investment Manager E-mail: sfournier@ciff.org
CHILDREN'S MERCY HOSPITALS AND CLINICS Kansas City, USA	**Dr Susan Abdel-Rahman** Director, Development Pharmacokinetic and Pharmacodynamic Core Laboratory E-mail: srahman@cmh.edu
CLINTON HEALTH ACCESS INITIATIVE (CHAI) 383 Dorchester Ave., Boston, MA 02127, USA	**Ms Nine Steensma** Programme Manager, Essential Medicines E-mail: n.steensma@gmail.com
COCHRANE INFECTIOUS DISEASES GROUP LIVERPOOL TROPICAL SCHOOL OF MEDICINE Pembroke Place, L3 5QA, United Kingdom	**Dr David Sinclair** Effective Health Care RPC E-mail: sinclad@liverpool.ac.uk
DARTMOUTH COLLEGE Hanover, NH 03755, USA	**Dr Lisa Adams** Assistant Professor Infectious Disease & International Health Dartmouth Medical School Email: lisa.v.adams@dartmouth.edu
DRUGS FOR NEGLECTED DISEASES INITIATIVE (DNDi) 15 Chemin Louis Dunant 1202 Geneva - Switzerland	**Dr Nathalie Strub-Wourgaft** Clinical Director E-mail: nstrub@dndi.org **Ms Janice Lee** Project Coordinator, DNDi Paediatric HIV Project E-mail: jLee@dndi.org
ECUMENICAL PHARMACEUTICAL NETWORK (EPN) Paul-Lechler-Street 24 72076 Tübingen, Germany	**Mr Albert Petersen** Pharmaceutical Aid Department Difäm, German Institute for Medical Mission E-mail: petersen.amh@difaem.de

PARTNER	REPRESENTATIVE
ELIZABETH GLASER PEDIATRIC AIDS FOUNDATION (EGPAF) Suite 200 Washington, DC 20036, USA WCC Centre 150 Route de Ferney CH1211 Geneva, Switzerland	**Mr Philip O'Brien** Executive Vice President of Communications, Advocacy, and Development E-mail: pobrien@pedaids.org **Ms Eliane Drakopoulos** Public Policy and Advocacy Officer E-mail: edrakopoulos@pedaids.org
EUROPEAN MEDICINES AGENCY (EMA) 7 Westferry Circus Canary Wharf London E14 4HB United Kingdom	**Mr Ralph Bax** Scientific Administrator Paediatric Medicines - Paediatrician Human Medicines Special Areas Sector E-mail: Ralph.bax@ema.europa.eu
INTERNATIONAL FEDERATION OF PHARMACEUTICAL MANUFACTURERS & ASSOCIATIONS (IFPMA) Chemin Louis-Dunnant 15 1211 Geneva 20, Switzerland	**Ms Elise Drouyer** IFPMA, Ch. Louis-Dunant 15, 1211 Geneva 20 E-mail: e.drouyer@ifpma.org
INTERNATIONAL PHARMACEUTICAL FEDERATION (Fédération Internationale Pharmaceutique - FIP) Andries Bickerweg 5, P. O. Box 84200 2508 AE The Hague, The Netherlands	**Mr Luc Besançon** Manager, Professional and Scientific Affairs Tel: ++ 31703021988 E-mail: luc@fip.org
INTERNATIONAL UNION OF PHARMACOLOGY INTERNATIONAL PAEDIATRIC ASSOCIATION (IUPHAR/IPA) P. O. Box 790 (Tukholmankatu 17) 00029 HUS Helsinki, Finland	**Dr Kalle Hoppu** Director, Poison Information Centre Helsinki University Central Hospital E-mail: kaarlo.hoppu@hus.fi
JOHNS HOPKINS UNIVERSITY (JHU) Johns Hopkins University School of Medicine & Bloomberg School of Public Health 600 N. Wolfe Street, Harvey 319 Baltimore, MD 21287, USA	**Dr Fizan Abdullah** Associate Professor of Surgery and International Health E-mail: fa@jhmi.edu
JOHN SNOW INC (JSI) 1616 Fort Myer Drive, 11th Floor Arlington, VA 22209, USA	**Ms Alexis Heaton** Technical Adviser E-mail: alexis_heaton@jsi.com

PARTNER	REPRESENTATIVE
MEDICINES FOR MALARIA VENTURE (MMV) International Centre Cointrin Block G, 3rd Floor Route de Pré-Bois 20 CH-1215 Geneva 15, Switzerland	**Mr George Jagoe** Executive Vice President - Global Access E-mail: jagoeg@mmv.org **Dr Florence Camus-Bablon** Consultant, MMV - paediatric treatment of non-complicated malaria in francophone Africa. +33 6 75 68 44 36; E-mail: fcb0305@hotmail.com
MÉDECINS SANS FRONTIÈRES (MSF) MSF OCG Rue de Lausanne 78 Case postale 116, 1211 Geneva 21	**Dr Anne Pittet** Pediatrician, responsible of paediatric training in MSF OCG E-mail: Anne.Pittet@geneva.msf.org
OXFAM 77 Lee Road, Blackheath London SE3 9EN, United Kingdom	**Mrs Philippa Saunders** **Consultant** E-mail: philippa.m.saunders@gmail.com
SPANISH AGENCY OF MEDICINES AND MEDICAL DEVICES Calle Campezo 1, Edificio 8 E-28022 Madrid, Spain	**Ms Belén Crespo Sánchez-Eznarriaga** Executive Director Tel: +34-609250445 E-mail: bcrespo@aemps.es
SWISSMEDIC Institut Suisse des produits thérapeutiques Hallerstrasse 7, Case postale, 200 Berne 9, Switzerland	**Dr Hans Stötter** E-mail: hans.stoetter@swissmedic.ch
THE GLOBAL FUND To Fight AIDS, Tuberculosis and Malaria Chemin de Blandonnet 8 1214 Vernier Geneva. Switzerland	**Ms Carmen Pérez Casas** Senior Technical Officer Global Health Supply Pharmaceutical Management Unit E-mail: carmen.perezcasas@theglobalfund.org
UNICEF Health Section – Programme Division UNICEF New York, USA UNICEF Supply Division Unicef Plads, Freeport 2100 Copenhagen, Denmark	**Dr Renee Van de Weerdt** Chief- Child Health and Emergency Response Email: rvandeweerdt@unicef.org **Mr Henrik K. Nielsen** Technical Specialist, Essential Medicines Medicines and Nutrition Centre E-mail: hnielsen@unicef.org **Mr Francisco Blanco** Chief, Medicines and Nutrition Centre E-mail: fblanco@unicef.org

PARTNER	REPRESENTATIVE
UNIVERSITY OF CALIFORNIA SAN FRANCISCO Suite 420, Box 0613 3333 California Street San Francisco, CA 94118 USA	**Dr Lisa Bero** Professor E-mail: berol@pharmacy.ucsf.edu
UNIVERSITY OF KWAZULU-NATAL PBag 7 Congella 4013 South Africa	**Mr Andy Gray** Senior Lecturer Dept of Therapeutics and Medicines Management Nelson R Mandela School of Medicine E-mail: graya1@ukzn.ac.za
UNIVERSITY OF LIVERPOOL and UK NIHR MEDICINES FOR CHILDREN RESEARCH NETWORK London, United Kingdom	**Dr Mark Turner** E-mail: mark.turner@liverpool.ac.uk

Ministry of Health:

MINISTRY OF HEALTH P. O. Box MB 582 Accra, Ghana	**Mrs Martha Gyansa-Lutterodt** Director of Pharmaceutical Services and Chief Pharmacist Tel/Fax: +233-302-666 366 E-mail: mlutterodt3@yahoo.com
TANZANIA FOOD AND DRUGS AUTHORITY P. O. Box 77150 Dar es Salaam, United Republic of Tanzania	**Dr Chukilizo NB** Tanzania Food and Drugs Authority E-mail: nchukilizo@yahoo.com

WHO Region:

WHO Regional Office for Africa (AFRO)	**Dr Jean-Marie Trapsida** Regional Adviser, EDM E-mail: trapsidaj@afro.who.int
Office of WHO Representative - Ghana 29 Volta Street, Airport Residential Area P. O. Box MB 142, Accra	**Dr Edith Andrews Annan** National Programme Officer E-mail: andrewsE@gh.afro.who.int **Dr Mary Nana Ama Brantuo** National Programme Officer E-mail: brantuom@gh.afro.who.int

WHO Headquarters:

HSS/EMP/Medicine Access and Rational Use	**Dr Clive Ondari, Coordinator, EMP/MAR** E-mail: ondaric@who.int **Dr Krisantha Weerasuriya, MAR** E-mail: weerasuriyak@who.int **Ms Lisa Hedman, MAR** E-mail: hedmanL@who.int **Ms Deirdre Dimancesco, MAR** E-mail: dimancescod@who.int **Dr Willem Scholten, MAR** E-mail: ScholtenW@who.int
HSS/EMP Quality Assurance and Safety: Medicines	**Dr Samvel Azatyan**, Manager MRS E-mail: azatyans@who.int **Ms Xiaoqiong Zheng, QSM** E-mail: zhengx@who.int
HIV Department	**Dr Shaffiq Essajee** E-mail: essajees@who.int
FCH/ Child and Adolescent Health and Development	**Dr Shamim Qazi, CAH** E-mail: qazis@who.int **Dr Wilson Milton Were, CAH** E-mail: werew@who.int **Dr Olivier Fontaine, CAH/NCH** E-mail: fontaineo@who.int
Roll Back Malaria Partnership Secretariat	**Dr Jan Van Erps, Coordinator** RBM Supply Chain Support E-mail: VanErpsJ@who.int
Stop TB Partnership Secretariat	**Dr Malgorzata Grzemska** Coordinator , Technical Support Coordination (TSC) E-mail: grzemskam@who.int **Ms Paloma Marroquin Lerga** Technical Officer, Global Drug Facility (GDF) E-mail: lergap@who.int