

UNICEF/WHO

**Priority Essential
Medicines for Child
Survival**

Copenhagen, Denmark

6-7 September 2010

This publication contains the Report of the WHO and UNICEF Preliminary Consultation to identify priority essential medicines for child survival and does not necessarily represent the decisions or policies of the World Health Organization or UNICEF

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Executive summary

A two day meeting on priority essential medicines for children, hosted by UNICEF Supply Division in collaboration with the World Health Organization (WHO), brought together experts in paediatric medicines from academia, the pharmaceutical industry (both innovator and generic), regulators, programme managers and implementers. The purpose of the meeting was to reach a consensus on what are priority essential medicines for children, and to identify the steps required to ensure that these medicines are available and affordable.

The aim of identifying a list of “priority medicines” is to focus policy makers, programme implementers, researchers, donors and the pharmaceutical industry on the medicines that will have the biggest impact on reducing child morbidity and mortality and to use the list as a means to build supply and regulatory capacity in countries. These priority medicines could be considered as the basic package for providing adequate care for children under 5 years of age.

Globally, the main causes of mortality and morbidity in children are pneumonia, diarrhoea, malaria, neonatal infections, HIV and TB. The list of priority essential medicines was identified based on the treatments needed for these conditions, current recommendations in WHO treatment guidelines and evidence for efficacy, including benefits measured as survival gain.

Product specifications were described for each priority medicine, as both 'base case' and 'best case' scenarios, to enable the development of the optimal dosage forms of these medicines for children. Specifications should include information about optimal packaging and pack size, taking account of the conditions in countries with high child mortality where supply systems are fragile, storage conditions are often not ideal, and human resources for health are limited. Health workers and caregivers require products that are easy to use, and children require medicines that address their special needs. Topics where more work and/or evidence are required before product specifications can be developed were also identified. The outcome of the meeting will be used as the basis for deliberations with the pharmaceutical industry, drug regulators, policy makers and implementers to make these priority essential medicines available and affordable.

The list of priority medicines for child survival was divided in two groups:

1. Products required and probably available in some countries already, although not necessarily in optimal pack sizes and strengths

Indication	Medicine
Pneumonia	<p>1. Amoxicillin: 250 mg and 500 mg dispersible, scored tablets or equivalent flexible oral solid dosage form (FOSD), in blister packs of 10</p> <p>Injectable antibiotics - but further work is needed to identify optimal strength and packaging. Currently available strengths listed.</p> <p>2. Gentamicin 5mg/ml, 20mg/ml</p> <p>3. Ampicillin 500mg, 1g</p> <p>4. Procaine benzylpenicillin, 1g</p> <p>5. Ceftriaxone 250mg, 1g</p>
Diarrhoea	<p>6. Oxygen - currently available, but further development of affordable delivery systems needed</p> <p>7. ORS: sachets for 200 ml; 500 ml and 1 L, appropriate flavour.</p>
Malaria	<p>8. Zinc: 20 mg scored dispersible tablet or FOSD.</p> <p>9. Artemisin combination therapy (ACT): strengths and combinations according to WHO treatment guidelines 2010, dispersible tablet or FOSD and dose optimized.</p> <p>10. Artesunate: 50-200 mg, rectal and injection dosage forms.</p>
Neonatal sepsis	<p>Injectable antibiotics, strengths as given above :</p> <p style="padding-left: 40px;">gentamicin</p> <p style="padding-left: 40px;">procaine penicillin</p> <p style="padding-left: 40px;">ceftriaxone.</p>
HIV	<p>11. Fixed-dose combination products as recommended in WHO treatment guidelines.</p> <p>12. Nevirapine: dosage form and strength for infants.</p> <p>13. Zidovudine: dosage form and strength for infants.</p>
Palliative care and pain	<p>14. Paracetamol (variable FSOD forms).</p> <p>15. Morphine.</p>
Child survival	<p>16. Vitamin A: 100,000/200,000 IU IU strength</p>

Products required, but for which further development is needed:

Indication	Medicine
Tuberculosis	<ol style="list-style-type: none">1. TB fixed-dose combination (FDC) products to deliver rifampicin: 15 mg/kg/d (10 to 20 mg/kg/day) isoniazid: 10 mg/kg/d (10 to 15 mg/kg/day) pyrazinamide: 35 mg/kg/d (30 to 40 mg/kg/day) ethambutol: 20 mg/kg/d (15 mg to 25 mg/kg/d). <p>Ideally a product needs to be developed that will deliver these doses when given in 0.5 to 2.0 'tablets' per day over the weight range, 5 - 30 kg, for example a FDC containing rifampicin 250 mg, isoniazid 150 mg, pyrazinamide 400 mg, and ethambutol 250 mg.</p>
HIV	<ol style="list-style-type: none">2. Isoniazid/co-trimoxazole as a fixed dose combination product for use in children with HIV, for prophylaxis of tuberculosis and PCP. Optimal strength and dosing regimen needs to be defined.
Neonatal care	<ol style="list-style-type: none">3. Caffeine citrate: 20 mg/ml liquid - a standard market product exists only in a limited number of markets.4. Chlorhexidine digluconate solution, 4% - a commercial product may be available, but the regulatory pathway needs to be determined and the optimal product types needs to be established.5. Vitamin K: optimal dose and strength of injection needs to be identified.

The meeting recommended the following next steps:

- Discuss the list of medicines with manufacturers at the UNICEF Pharmaceutical Manufacturers meeting on 27th-28th September 2010.
- Refine the complete descriptions of the products in the priority list-WHO/UNICEF.
- Identify the "pathways to registration" for each of the priority products and prepare a description of the pathway for all of them. This work might be done by the WHO Paediatric medicines Regulator Network (PmRN).
- Raise awareness of the importance of FOSD forms for children.
- Discuss the need for weight based dosing with programme managers.
- Identify if there is a suitable alternative to weighing scales for estimating weight.
- Encourage programme managers and procurement agencies to have a separate product category for medicines for children, including separate budget lines for these medicines.
- Identify a predictable funding source for the procurement of priority medicines for children globally and at country level.
- Promote commitments to fund the purchase of priority medicines for children by international organizations including GFTAM, UNITAID, PEPFAR, PMI, UNICEF.

- Develop estimates of demand for these products for Community Case Management. Estimates based on disease burden are not sufficient for industry; programme estimates are required to understand market demand.
- Developing an effective advocacy strategy, potentially including World Pneumonia Day 12th November 2010.

Key points from discussion

- Age-appropriate formulations of medicines for children are not always available.
- Liquid formulations can be difficult to use and store, which can make their use impractical in some areas.
- Solid formulations and flexible solid oral dosage forms, such as dispersible tablets, that can be given whole to older children or dispersed in water for ease of administration to younger children are preferred. However, this is provided they should be palatable and require minimal manipulation by health professionals or carers prior to use (i.e. flexibility/adaptability of the medicine to account for developmental and size differences, with the ability to reliably divide the unit dose).
- Medicines for children should contain as few excipients as possible, that are safe and non-toxic.
- Dosage forms need to be stable in a variety of climates, including Zone IV climatic conditions, easily transportable and low in bulk/weight and affordable.
- Appropriate packaging is a critical component of product development and presentation, to ensure product quality, safety and efficacy at time of dispensing and ease of use. Attractive packaging with simple pictorial instructions may improve use and compliance.
- From a public health point of view it may be necessary to accept some variability from the ideal dose in order to simplify dosing and administration instructions and to enable dosing by weight bands in children.
- There is a need to develop a method for estimating a child's weight accurately for settings where calibrated weighing scales are not readily available.
- It is important to consider the strength of the supply chain. The introduction of multiple products may overburden an already fragile supply chain. It would therefore be better to introduce one specialized product to meet all the needs of children.
- Innovative application of existing technology could address the short term needs of developing specialized products for children in resource poor settings.
- The necessity for rapid and affordable access to high quality essential medicines in resource poor settings increases the push for the adoption of flexible platform technologies.
- Early collaboration among all stakeholders is required to identify safe, efficacious and high quality medicines for children that need to be developed to ensure timely global access.
- International donors and governments may need to introduce incentives to stimulate R&D for paediatric medicines was raised.
- To make case for researching, developing and manufacturing medicines for the developing world, evidence is required that includes epidemiological studies estimates of burden of disease and demand forecast.

- Many of the priority essential medicines for child survival are off-patent and so there may be a role for other stakeholders, in addition to R&D companies, in the manufacture and supply of those medicines.
- It is feasible for generic companies to manufacture paediatric formulations and it could help with the affordability of high quality medicines.
- New regulatory pathways may need to be developed to enable generic manufacturers to develop new forms of products where there is no classic 'innovator'.
- In order to develop new formulations specific guidance from a market-influencer such as WHO/UNICEF is necessary to engage suppliers.
- A clear market need and a specific product profile is necessary to ensure the development of new paediatric products.
- The product profile requires a lot of specificity because any changes after commencement of the development process could add time and cost to the development process.
- There must be customers that are willing to pay more for a better product to achieve better treatment outcomes for children.
- To ensure a high quality product, the funding source for the development of the product must require a certain quality standard, otherwise manufacturers will not invest in better quality.
- The UNICEF/WHO Sources and Prices of Selected Medicines for Children can be used by programmes to identify potential sources for these medicines as it identifies manufacturers with local GMP.
- Customization of pharmaceutical products is a considerable investment and a balance is required between the gain achieved and the cost of the exercise.
- Before undertaking customization, need to define roles and responsibilities for the product development, be very specific about what is required and do not make changes once development is in progress, consider timelines involved, consider the production implications, such as type of machinery required and capacity to manufacture and quality assessment and regulatory implications.
- The success of MMV has shown that public private partnerships are a viable model for drug development and that specialized medicines for children can be developed and delivered to market.
- The European Medicines Agency (EMA) uses a combination of obligations and rewards to encourage the development of medicines for children. This strategy could be considered by other regulatory agencies.
- The paediatric use marketing authorization (PUMA) is for the development of better generics, e.g. a formulation specifically for children. To date not many applications have been received for the development of a paediatric specific product from generic manufacturers.
- Paediatric formulations are currently a priority for the prequalification programme.

- The WHO - UN prequalification program team can support companies to help build capacity for the manufacture of priority medicines.
- Using community health workers to provide curative services may generate high demand for the priority essential medicines for child survival.
- Understanding the behaviours and motivators of consumers and providers is key to improving standards of case management.
- The distribution of specialized medicines for children should be combined with a comprehensive communication strategy targeting caregivers and providers.
- Including the private sector will be important to help improve access to priority essential medicines for child survival.

Background

Improving child health is a global health priority. The global mortality rate in children under five years remains a significant and inequitable problem. Medicines for children have long been a neglected area. The World Health Organization recommends that children should be given medicines that have been appropriately evaluated and formulated for use in paediatric populations, as the pharmacokinetics and pharmacodynamics of drugs in children differ from those of adults and the accurate administration of medicines to children can be challenging. Since 2006, a lot of work has gone into identifying essential medicines for children and optimal paediatric dosage forms. The 1st WHO Model List of Essential Medicines for Children was published in 2007 and a 2nd revised edition in 2009. A WHO Model Formulary for Children has recently been published.

The meeting was chaired by Atieno Ojoo, technical specialist, pharmaceuticals, UNICEF SD and opened by Hanne Bak Pedersen, Deputy Director UNICEF SD, Copenhagen. It was highlighted that since the launch of the WHO Make Medicines Child Size Initiative in 2007, there has been good engagement between partners and increasing awareness among paediatric stakeholders regarding the specific requirements needed for paediatric medicines. However, despite recent figures showing that child mortality is decreasing, there is still a long way to go to reach the MDG 4 targets in many priority countries¹. Ensuring availability and access to priority essential medicines for the treatment of the major causes of disease in children will help countries reduce child mortality rates. It agreed that it is important at present to focus on the priority essential medicines that will contribute most to improvement in child survival.

Meeting objectives

The objectives of the meeting were to:

1. Agree a list of priority essential medicines for child survival.
2. Identify ways for improving access to these medicines at country level.
3. Define the best dosage forms of the priority medicines.
4. Identification of specific product gaps.
5. Develop a plan to fill the gaps in terms of new products, new formulations and potential sources.
6. Indicate to industry and donors where development and financing is required.

¹ UNICEF 2010. Progress for Children. Achieving the MDGs with Equity. Number 9, September 2010. http://www.unicef.org/media/files/Progress_for_Children-No.9_EN_081710.pdf

Summary of presentations

The presentations made at the meeting are available at: www.unicef.org/supply/index_56401.html. A brief summary of the key points is provided below.

What are the Priority Essential Medicines for Child Survival? (Shamim Qazi and Suzanne Hill)

WHO presented a proposed list of priority essential medicines for children. The aim of identifying a core group of “priority medicines” is to focus policy makers, programme implementers, researchers, donors and the pharmaceutical industry on the medicines that will have the biggest impact on reducing child morbidity and mortality and to use them as a means to build supply and regulatory capacity in countries.

Based on the major causes of disease in children, pneumonia, diarrhoea, malaria, neonatal infections, HIV, tuberculosis, current treatment recommendations in WHO guidelines as well as evidence for efficacy and survival gain, the list of potential priority essential medicines for child survival that were discussed at the meeting were:

- **ORS:** diarrhoea
- **Zinc sulphate:** diarrhoea
- **Oral amoxicillin:** pneumonia (fast breathing) and severe pneumonia in low HIV setting; pneumonia (fast breathing) in high HIV setting
- **Cotrimoxazole:** Pneumonia (fast breathing) in low HIV setting; prophylaxis in high HIV setting
- **Ampicillin + gentamicin:** severe pneumonia in high HIV setting and very severe pneumonia in both low and high HIV setting; neonatal sepsis
- **Ceftriaxone:** severe pneumonia in high HIV setting; very severe pneumonia in both low and high HIV setting; neonatal sepsis
- **Oxygen:** very severe pneumonia in both low and high HIV setting
- **Artemisin combination therapy:** uncomplicated malaria
- **Artesunate injection:** severe malaria
- **Artesunate rectal dosage form:** pre-referral treatment of severe malaria
- **Quinine injection:** severe malaria
- **Procaine penicillin + gentamicin:** neonatal sepsis
- **Chlorhexidine:** reduce neonatal sepsis through provision of perinatal care
- **Caffeine citrate:** to improve survival in preterm neonates with apnoea
- **Isoniazid:** long term prophylaxis for TB in children with HIV
- **Morphine:** pain relief and adequate palliative care
- **Paracetamol:** to manage mild pain in children
- **Vitamin A:** prevention of Vitamin A deficiency in children
- **1st line 4 drug and 3 drug FDCs for TB:** to ensure effective treatment and reduce risk of development of resistance

In developing product specifications, the meeting agreed on the following principles:

1. That weight based dosing should be used.
2. Simple dosing regimens should be preferred, i.e. once or twice daily administration wherever possible, and splitting tablets or other oral dosage forms into no more than 2.
3. Products should be of an appropriate strength and dosage form for children.
4. Use of strategies to enhance adherence through packaging and labeling should be encouraged.
5. Regulatory requirements need to be considered, including quality standards and pathways for registration.

Current challenges with developing medicines for children

Low demand for specially formulated medicines for children

In the absence of appropriate dosage forms of medicines for children, most end-users are used to making do with the medicines that are available. As a result, the administration of a medicine to a child often involves breaking an adult tablet into smaller pieces, then crushing and adding to food or liquid, leading to inaccuracies in dosing. Another problem is the expectation from both end-users and clinicians that medicines for children should be liquids as it is generally believed that children prefer liquids and weight based dosing is much easier with liquids. However, the accurate administration of a liquid medicine to a child is not assured even if the correct dose is calculated. There is evidence to show that measuring spoons and other devices supplied with liquid medicines are not accurate and that significant under- and over- dosing can occur^{2,3,4}. The WHO recommends Flexible Solid Oral Dosage (FSOD) forms as the optimum formulation for children's medicines administered via the oral route, as they have improved stability and shelf life over liquids and are less bulky to ship and store⁵. The demand for appropriate dosage forms of medicines for children from end-users and health workers needs to be increased.

Weight-based dosing

The majority of medicines for children require the dose to be calculated on a mg per kg basis. Although 'weight based' dosing is the gold standard, it is often not possible in resource poor settings due to a lack of calibrated weighing scales. If the dose cannot be accurately calculated there is a risk of under- or over-dosing which can lead to the development of drug resistance or toxicity respectively. There is an urgent need for a validated method for estimating weight accurately in paediatric populations in resource poor settings. Some medicines e.g. artemisin combination therapies (ACT) for the treatment of malaria, currently use age based dosing. In the case of Coartem®, the packs indicate

² Griefsmann K, Bretkreutz J, Schubert-Zsilavec et al. Dosing accuracy of measuring devices provided with antibiotic oral suspensions. *Paediatric and Perinatal Drug Therapy*. 2007; **8**: 61-70.

³ Falagas et al. 2010. Inaccuracies in dosing with teaspoons and tablespoons. *The International Journal of Clinical Practice*. **64**(9): 1185-1189.

⁴ Monk PM and Ball PA. The accuracy of a paediatric dosing device. *The Australian Journal of Hospital Pharmacy*. 1997; **27**: 323-324.

⁵ WHO technical report series; 958. *The selection and use of essential medicines: report of the WHO Expert Committee, March 2009*. Geneva, World Health Organization, 2009.

weight-based dosing, but national ministries of health often translate the weight bands into age bands for their national treatment guidelines. Ideally weight 'bands' recommended for doses of different medicines should be harmonized, so that all the priority medicines can be administered based on the same weight band system in order to simplify dosing calculations and reduce medication errors in children. Further work is required to determine whether this is feasible.

Strategies to enhance adherence

Poor adherence to treatment can lead to treatment failure and the development of drug resistance. Better packaging and labelling needs to be developed for children's medicines to help improve adherence.

Regulatory requirements

Changes in product specifications and packaging require regulatory approval. These issues will need to be addressed. Regulatory pathways need to be described for the changes to product specifications that may need to be undertaken to develop paediatric formulations.

Evidence, practice and factors affecting the choice of medicines for children, optimal dosage forms and dosage strengths

Health Worker Perspective (Kelita Kamoto)

Results from a recent qualitative survey of community health workers in Malawi were presented. The study was done to identify problems and preferences with the use of 4 medicines that are used for the treatment of malaria, diarrhoea and pneumonia in children: Artemisin Combination Therapies (ACT), ORS, cotrimoxazole and paracetamol. With respect to the taste and formulation, the general consensus was that under-5s found medicines in liquid form easier to take and health care workers found them easier to administer. The preference was for medicines in liquid form, although tablets that easily dissolved were an acceptable alternative, as were sachets containing granules that could be dissolved in water. It was reported that fruit flavoured medicines were preferred by children to non-flavoured or sour tasting medicines. Many of the health care workers reported challenges with administering adult tablets to children. Tablets have to be split in order to provide the correct dose for a child. Health care workers felt that the practice of breaking tablets, with or without a tablet splitter, led to many problems including: imprecise/wrong dosing, wastage (more likely to drop pills, incorrect splitting/crushing translates into losses), hygiene issues, and accountability (inventory management) problems. If splitting was necessary the preference was for scored tablets. With regard to packaging, blister packs of a full treatment course were preferred. It was noted that while blister packs may demand extra space, compared to having large containers of tablets (e.g. 500 or 1000 tablets per bottle), there were far more problems with the management of large containers of tablets, including inventory management issues, having to share the medicines from the same container between health care workers who require smaller quantities, contamination/losses and the extra time required to repackage and label and the frequent stock outs of dispensing pill bags. Preference was given to packaging with clear labels and illustrations on how and when to take the medicine; good examples were cited as the Coartem® and ORS (packaged by Population Services International). The results of a survey of children's experiences with products showed that children experienced positive conditioning when products had a

picture of a child on the packaging and the flavour of the tablet was pleasing to them e.g. orange flavour. Positive conditioning is significant in inducing appetite in low appetite children or drug averse children. When packaging is not appealing and/or the taste is not good, children receive negative conditioning.

Médecins sans Frontières (MSF): Field experience with paediatric medicines (Carine Werder)

MSF paediatric programmes provide treatment for all the usual childhood diseases, as well as specialized care for the treatment of malaria, TB, HIV, diarrhoeal diseases, respiratory tract infections, neglected tropical diseases and other infectious diseases, such as measles. It was highlighted that the provision of care is hampered by a lack of adequate formulations and combinations of medicines for children and the fact that the cost of medicines for children are often higher than those for adult formulations. The benefits of using fixed dose combinations (FDC), in terms of ease of use, reduced pill burden and improved compliance, for the treatment of tuberculosis, HIV and malaria in children were stressed. The advantages and disadvantages of different dosage forms were discussed. Although liquid formulations have traditionally been favoured for children, the problems with their use in the field included inaccurate dosing by caregivers, stability issues both during storage and in use (powders for suspensions often require refrigeration after reconstitution) and higher transportation costs. Tablets are more stable than other dosage forms, but swallowing is a problem, especially in younger children. Tablets are often not available in appropriate strengths for children, resulting in problems in prescribing and administration; many tablets are not scored to allow easy and accurate division if splitting is necessary, and there is a lack of data regarding bioavailability when tablets need to be crushed if other more suitable formulations are not available. For example, it has been shown that lopinavir/ritonavir has decreased bioavailability after crushing, but at the present time the tablets are too big for children to take. Dispersible tablets were favoured due to the fact that they can be swallowed whole or given as a suspension to a child who cannot swallow tablets. Suppositories have the advantage that they can be given to children when they are unable to swallow, although their stability in tropical climates is a problem and in some countries they are not culturally acceptable. The characteristics of good medicines for children for MSF programmes and settings were identified as:

- Ease of administration for children, care givers and prescribers.
- Clear, easily understandable labeling and instructions, especially when the medicines are being given in settings where the caregivers are largely illiterate.
- Dose and dosage form that allows treatment across a range of weight or age bands.
- Stability in Zone IV climatic conditions.

Commentary on consumer perspectives (Susan Whyte)

The following matters were identified as being important to consider:

- Health systems in low income settings are usually a mix of public and private, formal and informal sectors that supplement one another. Medicines may 'leak' out of the formal system into the informal sector and a high proportion of medicines are obtained outside the public sector from small private clinics, pharmacies or small drug shops run by people who function as "community health workers."

- Public health centres may have poorly trained staff, a lack of equipment and regular stock outs resulting in prescribing of medicines without proper diagnosis, using a 'syndromic approach' based on reported symptoms and not actual examination: This contributes to polypharmacy -for example, a child with a fever will be treated for both malaria and pneumonia. Due to stock rationing in the public sector, patients may not receive a full treatment course of a medicine and are required to buy the additional medicines from the private sector. Caregivers often cannot afford to buy a complete course of treatment.
- Supplies of medicines often come in big containers and the medicines are then dispensed to patients in cones of paper, with instructions for administration and duration of treatment are written on them. There is some evidence of preference for medicines packaged in a more 'sophisticated' way, such as blister packs or as capsules.
- The problem of calculating medicine doses for children was also raised. In many low-income settings the weight of a child cannot be obtained due to the lack of weighing scales in drug shops. Even health facilities often do not have or take the time to use calibrated weighing scales. The use of a simple tool such as "the Broselow Tape" was recommended but the tape needs to be validated in low income settings.
- Most medicines are administered to children in the home by parents/caregivers. Mothers are very used to crushing tablets and mixing with food. For the administration of tablets, they sometimes hold a child's nose to get them to take the medicine (as the child gasps for air the tablet goes down).
- Use of injections has particular significance as well as problems. They may be the preferred route of administration for a medicine because people have learned to value injections through experience with the formal health system where having a drip or an injection is perceived as more effective than a table. Sometimes injections are more suitable because children cannot tolerate oral medicines However, in many countries, community health workers and drug shop workers administer injections even though they are not licensed to do so. There are concerns about the safety of such practices, due to the risk of harm from unsafe injections especially if needles and syringes are being reused. However, interventions aimed at teaching them about safe injection practices may be limited to avoid being perceived as encouraging an illegal practice.

Supply chain and logistics perspective for paediatric medicines used in the community (Alexis Heaton)

Increasingly, community health workers (CHW) are providing care and treatment for a number of different conditions at the community level to increase access to treatments for , pneumonia, diarrhoea, malaria, and malnutrition and improvements in child health and survival. They are reaching children in the most hard to reach areas in a wide variety of settings and with a wide variety of products. However, CCM, and treatment at the community level in general, creates unique considerations for the medicines CHWs use. The community locations are remote and transit to resupply points can be long, with non-motorized means of transport used to move medicines from resupply points to the CHW. There is generally a lack of infrastructure and storage space with the CHW is limited; as a

result the medicines are often exposed to sunlight, heat and rain during transportation and distribution in the community.

Medicines need to be selected with the full supply chain and end user in mind. Community based treatment adds additional layers to the supply chain and medicines used in this setting often require different characteristics to those medicines used in hospitals and health facilities. For instance, CHWs may not see many paediatric cases in a month, therefore bottles containing 1000 tablets could lead to difficulties in tracking inventory, unnecessary wastage, or contamination over time. Medicines need to be packaged so that they are heat and moisture stable even after they are dispensed to the caregiver. They need to be in a formulation that is both child and supply chain friendly, ideally dispersible tablets that have been taste-masked to make them appealing to children and caregivers. The medicines must come in appropriate strengths and pack sizes to allow for easy dispensing and inventory management, such as packs providing a full course of treatment and/or blister strips and age appropriate strengths to avoid tablet splitting. They should be packaged with information and pictures so that caregivers are able remember instructions for administration.

Specifications for medicines: desired dosage strengths, dosage forms and pack sizes

Academia Perspective (Marcel de Matas)

As noted above, the needs for medicines for children include the improved palatability, accurate and flexible dosing, easy preparation and administration, stability at all levels of the supply chain, and use over a wide range of ages. Examples of specific problems include overcoming the bitter taste of anti-malarials used in children and developing palatable formulations of Zinc and ORS. Innovative application of existing technology could meet the short term needs for developing specialized products for children in resource poor settings. The use of fast-disintegrating multiparticulate systems and/or fast-dispersing mini-tablets produced from these particulates can provide a flexible platform for dosage form design for children. The necessity for rapid and affordable access to essential medicines in resource poor settings increases the emphasis for the adoption of flexible platform technologies. However, in the longer term there is the potential for the adoption of novel technologies from beyond the pharmaceutical sector. Future advances may include molecular biological approaches to taste masking e.g. biochemical bitterness blockers, polymeric systems for modified release of drugs in children, and dividable strips for flexible adjustment of doses for children of different age and weight. It is also likely that a wider range of excipients may be able to be used in neonates and infants through development of formulation databases, to increase information about approaches for dealing with challenging molecules such as those with low aqueous solubility.

Industry Perspective (Tom Sam and Christine Strunz-Lehner)

Research and development companies

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) established a paediatric task force (PTF) in 2008 to actively partner with WHO and other interested parties to help improve the availability of treatments appropriately adapted to meet the needs of children, especially for conditions/diseases prevalent in resource poor settings. Challenges for the global research and development of paediatric medicines have

been identified as technical, ethical and financial. Early collaboration among all stakeholders is required to identify treatments that to be developed and to establish how to develop them to ensure safety, efficacy and timely global access. It is important to note that the industry can only support a reasonable range of dosages and package sizes without compromising patient access at acceptable cost. It was acknowledged that this may not always lead to a 'gold standard' product, but was considered to provide better access to paediatric medicines. Public private partnerships (PPPs) were highlighted as an effective means of bringing together public sector, academic and private sector research institutions to contribute their respective expertise and strengths. It was highlighted that many of the essential medicines for child survival are off-patent and so there may be a role for other stakeholders in addition to R&D companies in the manufacture and supply of those medicines.

Generic industry

It is feasible for generic companies to manufacture paediatric formulations and it could help with the affordability of high quality medicines. However, manufacturers will require incentives to produce specialized products that can meet the requirements of highly regulated markets. Some concerns were raised regarding the lack of support from regulators for a non-originators approach, such as innovation of an existing generic product (new formulation/new packaging). It was also highlighted that the complexity for product development in this manner may require a new regulatory pathway.

Ways of increasing the supply base for the priority medicines

Perspective from the Clinton Health Action Initiative (David Rupin)

The goal of the Clinton Health Action Initiative is to encourage the development and commercialization of paediatric friendly formulations and to improve access to optimal products at the lowest sustainable price, with a stable supply to the market. Experience from the UNITAID paediatric HIV program has shown that in order to develop new formulations, specific guidance from a market-influencer is necessary to engage suppliers. The WHO paediatric working group for HIV medicines gave clear guidance for what was needed. Following their recommendations, 21 new formulations have been developed since 2008. Before 2005, only 4 paediatric tablet formulations existed. In the case of FDCs for the treatment of tuberculosis in children there have been problems with development, because the treatment guidelines have changed. It was not clear what was required and so manufacturers were wary of investing in a 3-5 year development process for something that may not have a market at the end of the process. These experiences highlight the importance of knowing what is required and the expected market size. Projected volumes need to be sufficient for recovery of cost of development and ongoing profit and there is a need to have a funding source in place for the procurement of the end product. A clear market need and a specific product profile is necessary to ensure the development of new paediatric products. Information required for product specifications includes:

- Drug name
- Dosing schedule
- Dosage strength - pack size, tablet size, if scoring is needed
- Attributes - dispersible, crushable, sprinkles etc

- Price target/tolerance
- Quality standard
- Shelf life - 3 to 5% of products in the field expire before use. Longer shelf life is preferred for logistical reasons.

A product profile requires specificity because any changes after starting the development process could add time and cost to development and in some cases could require restarting the whole process. Knowing the expected target price is important because a product could be developed, but it might be too expensive relative to existing products. It is important to know the quality standard required as this defines all the activities required for development, such as GMP, stability of product and bioequivalence. In the process there is also a need for market guidance. Too many of the same products on market can lead to confusion, especially if they are not interchangeable. If several different formulations of a single drug are available and recommended, orders for any one product may not meet a minimum order size; procurement managers may order the wrong product and there is potential for dosing confusion by health care workers and patients. Also a small market share may dissuade suppliers from investing in the development of new, superior products for children. The funding source for development of the product should require a clearly articulated quality standard; otherwise manufacturers will not invest in better quality.

UNICEF perspective (Francisco Blanco)

Since 1999, UNICEF in collaboration with the WHO and other partners has provided information on the sources and prices of medicines for emerging programmes, such as HIV/AIDS and Malaria. In 2009, the first edition of the sources and prices of selected medicines for children was published, listing 77 medicines and their formulations; the majority were selected from the WHO Model List of Essential Medicines for Children. It contained information regarding their indicative prices, contact information for manufacturers and registration information. The publication was used to update the UNICEF supply catalogue, provide information for country programmes and to identify new sources for those products for which limited suppliers had previously been found. An updated 2nd edition has recently been published, with 240 medicines in 612 different paediatric formulations, including new sections for pain and palliative care and neglected tropical diseases. However, for 144 products no sources were identified; these were mainly those available from limited sources in developed markets. The launch of the publication was an opportunity to advocate for increased access to medicines for children. Information about manufacturers and products can assist programmes to identify potential sources, but it is insufficient to address challenges in selection of products and procurement. A limitation with the data is that it only captures manufacturers who respond to the survey, therefore not all manufacturers are identified. There is a need for more information on product characteristics to guide selection for specific programmes and more information is required regarding regulatory approvals for certain products.

UNICEF's traditional approach to procurement of medicines was to standardize rather than customize, as customization of pharmaceutical products is a considerable investment and a balance is required between the gain achieved and the cost. Costs include the additional investment to ensure quality, loss of speed and flexibility and the regulatory implications of any changes. However, these must be weighed against the impact of improved treatment

compliance, donor/partner visibility and market development. Recent examples where UNICEF has customized products include artesunate + mefloquine co-blisters for Cambodia with specific packing instructions in English and Kher and Amoxicillin dispersible tablets for Uganda. Challenges encountered during the customization process included extended timelines. For the artesunate + mefloquine co-blisters the planned process time was 29 weeks (7.5 months), but it actually took 15 months. Due to constant changes to the product specification for the dispersible amoxicillin, the planned delivery date for the product has slipped from March 2010 until October 2010. Before undertaking customization, need to define roles and responsibilities for the product development, be very specific about what is required and do not make changes once development is in progress, consider timelines involved, consider the production implications, such as type of machinery required and capacity to manufacture and quality assessment and regulatory implications.

Perspective from Medicines for Malaria Venture (Penny Grewal)

Medicines for Malaria Venture (MMV), a not-for-profit research foundation established in Switzerland in 1999 has been working over a decade to discover, develop and deliver new medicines for malaria with public, private and philanthropic sector partners.

It has a large antimalarial pipeline with over 50 projects, from those in discovery to several in Phase III/IV clinical trials. The success of MMV's partnership model has been proven with the co-development and launch of its first product, the paediatric antimalarial Coartem® Dispersible with Novartis (first registration with Swissmedic). All MMV products are developed to international ICH standards. It has also submitted two new antimalarials to the European Medicines Agency (EMA) for regulatory approval with Sigma Tau Pharma (EMA orphan drug) and Shin Poong Pharmaceuticals (EMA Article 58).

The launch of artemether + lumefantrine dispersible, a paediatric formulation manufactured by Novartis, exemplifies MMV's responsiveness to the urgent need for child-friendly antimalarials. Children find the tablet easy to take as it disperses in a little water, has a sweet cherry flavour, and is not at all bitter like its parent drug and other artemisinin-based therapies. The flavour was chosen following a survey of children's taste preferences and innovative pictorial packaging, to ensure correct dispensing and use, was tested in the field for cultural acceptability and comprehension.

The development of a child-friendly formulation is complicated and benefits from some degree of cost sharing with industry partners. As MMV's successful development of artemether + lumefantrine dispersible with its partner Novartis clearly demonstrates, specialized antimalarials for children can be developed and delivered to market.

MMV is currently working with its partners on paediatric formulations of their late-stage products. As part of the contractual process, the development partner agrees to obtain stringent regulatory approval, provide the product at a low price for the public sector and register the product in malaria-endemic countries.

Developing an appropriate paediatric formulation does not guarantee uptake in countries due to various barriers involving policy change processes and information sharing. MMV recognizes that more work is required to overcome such barriers as well as ensure that child-

friendly medicines are considered a special product category when ministries select products. This will ensure that children benefit from products developed specifically for them.

Regulatory Incentives: Experience from the European Medicines Agency (Nathalie Seigneuret)

The objective of the European paediatric regulation is to improve the health of children by increasing high quality and ethical research into medicines for children, increasing availability of authorized medicines for children and increasing information on medicines. The pillars of EU paediatric regulation consist of a paediatric committee, a paediatric investigation plan (PIP), a system of obligations and rewards and transparency measures. The Paediatric Committee consists of representatives from each EU Member State, covering a wide range of expertise relevant to paediatrics, as well as representatives from parents/patients and healthcare professionals. The committee set up 3 working groups: one for formulations, one for non-clinical topics and an extrapolation group to help with the evaluation of the Paediatric Investigation Plans (PIPs). The PIP gives details of the timing and measures that are necessary to obtain a paediatric indication for a product with an age appropriate formulation in all paediatric subsets affected by the condition – what is required for market authorization. Waivers can be given if it can be shown that the product being developed has no role in the treatment of children. Waivers are product specific and can be “total” i.e for all paediatric age subgroups for the conditions/indications being applied for; a “partial waiver” for one or more subsets and/or indication(s), but a PIP is still required. There is also a “class waiver” for a class of products in a condition, or for all products aimed at a condition. A list for these has been adopted by the Paediatric Committee.

There are certain obligations in the EU paediatric regulation system. For currently unauthorized medicinal products applicants need to submit the results of studies carried out according to the agreed PIP at the time of the marketing authorization application or the approved waiver/deferral. Authorized patented medicinal products require the results from studies according to the agreed PIP at the time of application for a new indication, new route of administration, new formulation or a waiver/deferral. Orphan medicinal products have the same obligations. Off-patented medicinal products are assigned what is known as paediatric use marketing authorization (PUMA). This is optional and covers paediatric indications and formulations. The PUMA is essentially for the development of better generics, e.g. a formulation specifically for children. To date not many applications have been received for the development of a paediatric specific product from generic manufacturers. Rewards are given for all PIPs correctly completed. However, a product specific or class waiver does not trigger a reward and inconclusive studies in a PIP or negative PIP results do not receive a reward.

Prequalification of Medicines Programme (Lembit Ragö)

The objectives of the prequalification (PQ) programme are to propose a list of prequalified products and manufacturers that meet international norms and standards, where the quality, efficacy and safety has been assessed, inspected and controlled. Through the programme help is provided to national drug regulatory authorities to help build capacity in assessment, inspection and control to enable them to meet international norms and

standards. Customized technical assistance can also be provided to develop local production and capacity for clinical studies. Technical assistance is provided separately to the assessment /inspections process and this is free of charge to interested and committed companies. A study of antimalarial medicines has shown that PQ status can make a difference. Prequalified antimalarial medicines rarely failed quality control testing, whereas non-PQ products often did. To date 46 paediatric products have been prequalified (38 anti-HIV; 3 anti-TB; 4 antimalarials; 1 anti-influenza), 23 are under assessment (11 anti-HIV; 5 anti-TB; 6 antimalarials and 2 Zinc products). Training, advice and assistance have and will continue to be provided to companies that have shown an interest and commitment to prequalify paediatric formulations. In cooperation with applicants the PQ programme hopes to facilitate the prequalification of more paediatric formulations. The joint product assessment approach between WHO PQ and drug regulators from developing countries is designed to facilitate mutual regulatory recognition. This approach could be used for the priority essential medicines for children.

Ways of increasing demand for high-quality appropriately formulated essential medicines for children

UNICEF Programme Division perspective (Ahmet Afsar)

Community case management (CCM) involves the provision of curative services, preventive services and health promotion activities by community health workers (CHW). Many of the CHWs are volunteers, although others receive salaries or some other form of financial compensation. They are trained in the diagnosis and treatment of common childhood illnesses and are provided with medical supplies to support their work. However, their training is not standardized and varies greatly from country to country. Inventory control at this level is often weak due to a lack of a standard reporting system and high rates of illiteracy. The logistics of getting the supplies out to remote areas are complicated. Often there are no roads and non-motorized means of transport are used to collect the medicines and bring them back to the community. Medicines will often be stock piled, which leads to wastage when the products ultimately expire. CHWs are meant to be regularly supervised by local health centre staff, however, this does not always happen because the health centre workers have heavy work-loads and cannot often travel out to the remote areas. Demand for essential medicines for children will increase as support for community case management grows. However, commitment to CCM will require policy changes at both the global and country level. Starting a programme can be a slow process, involving the need for lobbying, collaboration and consensus from development partners and UN agencies.

Social Marketing Approaches to Child Survival (Angus Spiers)

Population Services International (PSI) is a global health organization with programs targeting malaria, child survival, HIV and reproductive health. They work in partnership within the public and private sectors, and use social marketing approaches to supply medicines the world's most vulnerable populations. They currently supply 3 customized products for children. A diarrhoea treatment kit, consisting of a bundle of low-osmolarity ORS and 10 zinc tablets; pre-packaged therapies for pneumonia (PPT): containing the first line antibiotics according to the local policy (either amoxicillin or cotrimoxazole) and pre-packaged ACTs according to WHO prequalified first line therapy. Medicines are customized to the market and the audience making them more recognizable and approachable. Before

supplying medicines in a country, formal approval to distribute them is obtained from the local Ministry of Health. Field experience has shown that using branding and attractive packaging with simple instructions has a positive effect on consumer recall and compliance. In settings with high rates of illiteracy, pictorial instructions help caregivers identify the correct dosing regimen. When the packaging cannot be changed there is a need to identify novel approaches to improve dispensing and administration, such as the use of pharma (dispensing) bags. The price of each medicine should always be based on willingness to pay data. As much as possible PSI seeks to align their branded medicine to the lower end of the price range. The main route for delivery is through private sector pharmacies and community-based service delivery. The distribution of the medicines is combined with a comprehensive communication strategy targeting caregivers. This aims to develop awareness of major childhood illnesses and the availability of an effective treatment and to motivate them to seek appropriate care in a timely manner. Health care providers should also be included in any communication initiatives.

Product specifications for the priority essential medicines

Product specifications were described and drafts prepared for each priority essential medicine, as both a base case and a best case scenario, to enable the development of the optimal strength and formulation for children. The profiles should include information about optimal packaging and pack size, based on the premise that in countries with high child mortality supply systems are fragile, storage conditions are often not ideal, and human resources for health are limited. It was also stressed that health workers at all levels and caregivers require easy to use products and children require medicines that address their special needs. These product profiles require further consultation before final publication, but it was agreed that this should be done as a priority.

Following small group discussions and feedback to all meeting participants a list of "sure" priority medicines for child survival was agreed upon. Areas where more work or evidence was required before product specifications could be made were then identified. These products are listed in Table 1, executive summary.

Further work required

Antiretroviral fixed-dose combinations: products should be based on the latest guidelines. Some products already exist and the base case is much better than for the majority of the other priority medicines. At the present time at least 3 different 1st line treatments are available that satisfy treatment requirements for most countries. The best case scenario is for "made to measure" combinations specifically for countries. There is a need for a correct dosage form and pack size for the Prevention of Mother-to-Child Transmission of HIV (PMTCT). There is also a need for products and specifications for infants to prevent transmission. Need to identify what is required in terms of formulations for younger children. There is also a need to limit the different number of regimens being recommended.

Antituberculous fixed-dose combinations: a product is needed that allows simplified dosing across all weight bands. The existing FDC products require combinations of multiple tablets and strengths to achieve the correct dose for children.

Caffeine citrate: a standard product is required. Market readiness needs to be assessed. There is a need to build demand in countries by undertaking market sensitization and product familiarization with policy makers and end users.

Chlorhexidine: The concentration is critical to efficacy, which suggest that it should be assess as a pharmaceutical product. The appropriate regulatory pathway needs to be identified and an ideal patient pack developed.

Isoniazid/cotrimoxazole: There may be needed for development of a FDC product for prophylaxis against pneumonia and TB in HIV positive children. Optimal disease and strengths of the components would need to be defined.

Clinical evidence needed

Further evidence is required to identify the optimum doing regimens for:

- Gentamicin.
- Ampicillin.
- Procaine penicillin.
- Ceftriaxone.
- Vitamin K.

Annex 1: List of presentations

The following presentations were made and are available at:
http://www.unicef.org/supply/index_56401.html

- *Dr Shamin Qazi Ahmed, Child and Adolescent Health, WHO, Geneva*
Medicines recommended to prevent and manage the priority diseases at the community and health facility level
- *Dr Suzanne Hill, Essential Medicines and Pharmaceutical Policies, WHO, Geneva*
Medicine gaps identified for each disease area (missing medicines, missing formulations, missing pack sizes)
- *Dr Kelita Kamoto, Director, Health Technical Support Services Ministry of Health, Malawi*
Product Characteristics: Perspectives from Community Health Workers in Malawi
- *Carine Werder, Medicins Sans Frontieres*
Paediatric Medicines: MSF field experiences
- *Susan Foster, Tufts University, Boston, USA*
Amoxicillin Formulations in the Field
- *Susan Reynolds Whyte, Copenhagen University*
Commentary on consumer perspectives
- *Tony Nunn, Clinical Director of Pharmacy, Alder Hey Children's NHS Foundation Trust*
Overview of some of the dosage form issues and gaps
- *Alexis Heaton, John Snow International Inc, Washington D.C., USA*
Characteristics of Paediatric Medicines: the supply chain perspective
- *Dr Marcel de Matas, Institute of Pharmaceutical Innovation, University of Bradford, Bradford, UK*
Formulating Drug Products for Children in the Developing World: an academic perspective
- *Dr Tom Sam (Director Pharmaceutical CMC, Merck Manufacturing Division), IFPMA*
Research and Development Pharmaceutical Industry Perspective on Specifications for Pediatric Medicines
- *Christine Strunz-Lehner (Sandoz GmbH, Austria), European Generics Association*
Developing paediatric medication - learning's from a generic pilot project
- *David Ripin, The Clinton Health Action Initiative*
Pediatric Formulations: Challenges and Barriers to Access

- *Francisco Blanco, Chief, Medicines and Nutrition Center, UNICEF SD, Copenhagen*
Sources and Prices of Medicines for Children
- *Penny Grewal, Director, Medicines for Malaria Venture Access and Delivery*
Increasing the supply base of paediatric antimalarials: MMV case study
- *Henrik Nielsen, Technical Specialist, Essential Medicines Unit - Medicines and Nutrition Centre, UNICEF SD, Copenhagen*
Procurement process of tracer medicines (Amoxicillin and others)
- *Nathalie Seigneuret, European Medicines Agency, London, UK*
Regulatory incentives: Experience from European Medicines Agency
- *Dr Lembit Rago, Quality Assurance and Safety: Medicines (QSM), Department of Essential Medicines and Pharmaceutical Policies (EMP), Geneva*
Prequalification of Medicines Programme
- *Dr Ahmet Afsar, UNICEF PD, New York*
Demand creation: Commodity case management experience from Catalytic Initiative/HSS Program
- *Angus Spiers, Population Services International (PSI)*
Social Marketing Approaches to Child Survival

Annex 2: List of participants

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Nathalie **Seigneuret**, PhD, Scientific Administrator, Paediatric medicines, European Medicines Agency, London, UK

Prashant **Sisodia**, Export Manager, Cipla Ltd, Mumbai Central, India -- Did not attend

Angus **Spiers**, Deputy Director, Malaria control, Malaria and Child Survival Dept, Population Services International, Nairobi, Kenya

Rebecca **Stevens**, Director of Public Affairs, Malaria Initiatives, Novartis International AG (IFPMA) -- Did not attend

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