

Scaling-up co-trimoxazole prophylaxis in HIV-exposed and HIV-infected children in high HIV-prevalence countries

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Lancet Infect Dis 2007; 7: 686–93

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Co-trimoxazole (trimethoprim-sulfamethoxazole) is a widely available antibiotic that substantially reduces HIV-related morbidity and mortality in both adults and children. Prophylaxis with co-trimoxazole is a recommended intervention of proven benefit that could serve not only as an initial step towards improving paediatric care in young children with limited access to antiretroviral treatment, but also as an important complement to antiretroviral therapy in resource-limited settings. Despite co-trimoxazole's known clinical benefits, the potential operational benefits, and favourable recommendations by WHO, UNAIDS, and UNICEF, its routine use in developing countries—particularly sub-Saharan Africa—has remained limited. Out of an estimated 4 million children in need of co-trimoxazole prophylaxis (HIV-exposed and HIV-infected), only 4% are currently receiving this intervention. We discuss some of the major barriers preventing the scale-up of co-trimoxazole prophylaxis for children in countries with a high prevalence of HIV and propose specific actions required to tackle these challenges.

Introduction

At the end of 2006, there were an estimated 2·3 million children worldwide living with HIV, an estimated 530 000 new HIV infections occurred, and 380 000 children died from AIDS.¹ An estimated 780 000 children are in urgent need of antiretroviral therapy (ART) and this number is constantly increasing.^{2,3} Most of these children live in sub-Saharan Africa, where only 10% currently access treatment.^{2–6} Despite the growing intensity of current efforts to offer ART to children living in resource-limited settings, substantial obstacles remain, which include: limited training and experience of providers in treating children; the lack of practicable, easy-to-use paediatric antiretroviral formulations; no fixed-dose combinations making treatment more difficult to administer and adhere to;⁷ the high cost of paediatric antiretroviral drugs that may be up to ten times more expensive than the corresponding adult formulations;⁸ and the lack of affordable and simple technologies for confirming HIV infection in children under 18 months of age. It is therefore likely to be some time before infrastructure and resources permit many more children to access life-saving ART.

In the meantime, co-trimoxazole (trimethoprim-sulfamethoxazole) is a recommended intervention of proven benefit that could improve paediatric care in young children and act as an important complement to ART in resource-limited settings.

Benefits of co-trimoxazole prophylaxis in HIV-infected infants and children

Co-trimoxazole is a widely available, easy to administer, safe, and low-cost antibiotic that still appears as a first-line drug on formularies of developing countries. It has a broad-spectrum prophylactic action against common bacterial pathogens, *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*), and protozoa such as *Plasmodium* spp and *Isospora belli*. Randomised controlled trials (RCTs)^{9,10} and studies with historical controls^{11–16} in HIV-infected African adults consistently show significant

benefits in survival for those receiving co-trimoxazole prophylaxis. These improvements in survival have been accompanied by substantial reductions of severe disease events and the number of hospital admissions linked to invasive bacterial disease, pneumonia, malaria, and diarrhoea, although disease-specific benefit has varied between studies.^{9,10,14,16} The only RCT done in children was in HIV-infected Zambian children aged 1–14 years, which found a highly significant benefit of co-trimoxazole in improving survival and reducing hospitalisations and pneumonia (hazard ratio 0·57 [95% CI 0·43–0·77], $p=0\cdot0002$).¹⁷ Many of the studies showing benefit have been in communities where in-vitro co-trimoxazole resistance to common bacterial isolates is already high.^{14,16–18}

It is well recognised that *P jirovecii* is a common cause of pneumonia and death in HIV-infected infants.^{19–22} The introduction of routine co-trimoxazole prophylaxis for infants at risk of HIV infection in several countries has been very effective in preventing *P jirovecii* pneumonia, which could in itself prevent a third to a half of all HIV-related deaths in African infants.²³

In addition to the clinical benefits of co-trimoxazole, there are several potential operational advantages. First, mothers are more likely to bring children to health-care centres for HIV testing and follow-up care if they know that an effective treatment is immediately available. This could also provide an opportunity to address HIV-related prevention and care issues for the mother and other family members. Second, co-trimoxazole prophylaxis provides an opportunity for systematic care of children at health facilities at lower levels of the health system and the observed stabilising effect on immune function and viral replication has the biological potential to delay the need for ART until it is available.¹⁴ Third, co-trimoxazole could serve as a backbone for establishing and strengthening a chronic care infrastructure upon which interventions including ART could be built, since systematic delivery of co-trimoxazole requires a health-care delivery system that will not only identify HIV-

infected children but also ensure that they remain in the system. Fourth, co-trimoxazole prophylaxis provides an opportunity to model drug adherence approaches before starting ART.^{24,25} Finally, co-trimoxazole prophylaxis is cost-effective and could have important benefits for other family members.^{26,27}

Co-trimoxazole has known clinical benefits, potential operational benefits, and is also recommended by WHO, UNAIDS, and UNICEF^{23,28} for all HIV-exposed and HIV-infected children until reliable confirmation of HIV status has been made. However, the drug's routine use in resource-limited settings—particularly sub-Saharan Africa—has remained limited. Out of an estimated 4 million children who are in need of co-trimoxazole prophylaxis (HIV-exposed and HIV-infected), only 4% are currently receiving this intervention.²⁹ We discuss some of the major barriers preventing the scale-up of co-trimoxazole prophylaxis for children in countries with a high prevalence of HIV and suggest specific actions to tackle them. Although these actions are proposed for high-prevalence, resource-limited settings, they may be more widely relevant.

Barriers preventing scale-up of co-trimoxazole prophylaxis in infants and children

Hypothetical objections against widespread use of co-trimoxazole in high HIV-prevalence countries

Scaling-up co-trimoxazole as part of the minimum package of care in Africa was initially hampered by a number of legitimate concerns. The provisional WHO/UNAIDS recommendations for Africa released in 2000³⁰ were made on the basis of two studies,^{9,10} both from Abidjan, Côte d'Ivoire, where at the time prevalence of bacterial resistance to co-trimoxazole was low. Clinicians and policymakers in Africa therefore doubted the efficacy of co-trimoxazole in countries where co-trimoxazole resistance was known to be high, and so did not accept or apply the provisional recommendations. Since then, several studies have shown that co-trimoxazole prophylaxis improves survival and reduces serious disease events even in areas of Africa where in-vitro co-trimoxazole resistance is common.^{12–17} Furthermore, although resistance levels increase with time, as they have in Abidjan, this has not prevented the drug from being useful.¹⁸ Co-trimoxazole's efficacy against pneumocystis, isospora, and malaria might explain its favourable effects on morbidity and survival in endemic areas.

Other major concerns of co-trimoxazole prophylaxis were that widespread use of the drug would accelerate the spread of multidrug resistance among common bacterial pathogens and increase resistance of *Plasmodium falciparum* to sulfadoxine-pyrimethamine and other antifolate antimalarial drugs. From a broader public-health perspective, this could mean reducing useful life of cheap and available first-line therapies; from the individual clinical management perspective there are

concerns that, for example, a patient with malaria would be more likely to fail treatment with sulfadoxine-pyrimethamine if already taking co-trimoxazole prophylaxis. However, an RCT in children aged 5–15 years in Mali showed that co-trimoxazole prophylaxis does not appear to select for sulfadoxine-pyrimethamine-resistant *P. falciparum*.³¹ Furthermore, since sulfadoxine-pyrimethamine is being phased out and replaced by more effective artemisinin-based combination therapies in most countries, concerns about antimicrobial resistance to sulfadoxine-pyrimethamine might become less relevant.

By contrast, uncertainty remains about the possible impact of co-trimoxazole prophylaxis on the prevalence of antibiotic-resistant bacteria, with studies so far showing conflicting results for enteric isolates.^{29,32} Since most of these studies were not specifically designed with the primary intention of studying drug resistance as a function of prophylaxis, the evidence base is not powerful enough to dismiss the risk of resistance developing, and specific ongoing surveillance is therefore justified. The potential problem is not only for increased resistance to co-trimoxazole, which is already high in many settings, but also for worsening resistance to other antibiotics.³³ However, co-trimoxazole prophylaxis may protect against development of resistance if it reduces the number of hospital admissions and the frequency of use of other antibiotics.

Actions required

There is a need for consultative forums within countries that bring together key stakeholders at a national level, to disseminate information on current evidence, bridge gaps in knowledge, allay fears on use of co-trimoxazole at country level, and present the rationale for current recommendations.²⁹ The forums should also serve to boost leadership and to prepare the next steps for implementing a phased national co-trimoxazole scale-up plan that is integrated into child survival programmes. Focus should be placed on the following: a national coordination mechanism that is inclusive of all major actors; a district and facility-based scale-up plan that includes a clear definition of needs, targets, and required budgets; a national drug procurement and distribution system that includes drugs and commodities for paediatric care including co-trimoxazole; and a system of monitoring the number of adults and children accessing co-trimoxazole, which will be needed for forecasting drug orders.

There is undoubtedly international importance in setting up surveillance monitoring programmes to follow microbial resistance emergence (eg, in enteric bacteria, *Plasmodium* spp, and pneumocystis) and to assess the ongoing efficacy of widespread co-trimoxazole prophylaxis programmes. Research is also needed to evaluate the efficacy of other antimicrobial agents for reducing morbidity and mortality of HIV-related

Panel 1: Initiation of co-trimoxazole prophylaxis in infants and children*

HIV-exposed infants and children†

Co-trimoxazole prophylaxis is universally indicated, starting at 4–6 weeks after birth and continued until cessation of risk of HIV transmission and exclusion of HIV infection

Infants and children with confirmed HIV infection‡

Infants aged less than 1 year

Co-trimoxazole prophylaxis is indicated regardless of CD4 percentage or clinical status§

Children aged 1–4 years

Co-trimoxazole prophylaxis is indicated for (1) WHO clinical stages 2, 3, and 4 regardless of CD4 percentage or (2) any WHO clinical stage (1–4) and CD4-cell count less than 25%

Children aged 5 years or more

Co-trimoxazole prophylaxis is indicated for (1) WHO clinical stage 3 or 4 regardless of CD4 level or (2) any WHO clinical stage and CD4-cell count less than 350 cells/μL¶

Universal option

Prophylaxis for all infants and children born to mothers confirmed or suspected of living with HIV. This strategy may only be considered in settings with a high prevalence of HIV, high infant mortality caused by infectious diseases, or limited health infrastructure

*Adapted from WHO guidelines.²³ †Defined as a child born to an HIV-positive mother or a child breastfeeding from an HIV-positive mother until HIV exposure stops (6 weeks after complete cessation of breastfeeding), and infection can be excluded. ‡In children younger than 18 months, HIV infection can only be confirmed by virological testing. For children older than 18 months, HIV infection can be confirmed by HIV antibody testing. §Once a child is started on co-trimoxazole, treatment should continue until 5 years of age regardless of clinical symptoms or CD4 percentage. Specifically, infants who begin co-trimoxazole prophylaxis before the age of 1 year and who subsequently are asymptomatic and/or have CD4-cell count $\geq 25\%$ should remain on co-trimoxazole prophylaxis until they reach 5 years of age. ¶Countries may choose to adapt a CD4 threshold of 200 cells/μL where *Pneumocystis jirovecii* and toxoplasmosis are the major targets for co-trimoxazole prophylaxis and where bacterial infections and malaria are not prevalent.

Panel 2: Recommendations for discontinuing co-trimoxazole in infants and children*

HIV-exposed children

Discontinue co-trimoxazole prophylaxis after HIV infection is excluded†

Infants and children with HIV‡

Until age 5 years

Maintain co-trimoxazole prophylaxis irrespective of clinical and immune response

Over age 5 years

Reassess and consider discontinuation on the following grounds:

CD4 testing not available:

- Do not discontinue co-trimoxazole prophylaxis, particularly in settings where bacterial infections and malaria are common HIV-related events
- Consider discontinuing co-trimoxazole prophylaxis in children with evidence of good clinical response to ART (absence of clinical symptoms for at least 1 year of therapy), good adherence, and secure access to ART

CD4 testing available:

- In countries where co-trimoxazole prophylaxis is recommended only for preventing *Pneumocystis jirovecii* and toxoplasmosis, it can be discontinued with evidence of immune recovery on ART (CD4-cell count ≥ 200 cells/μL after at least 6 months of ART)
- In countries with a high prevalence of bacterial infections and malaria, discontinue co-trimoxazole prophylaxis in children with evidence of immune recovery related to ART (CD4-cell count ≥ 350 cells/μL after at least 6 months of ART)

ART=antiretroviral therapy. *Adapted from WHO guidelines.²³ †In children younger than 18 months, HIV infection can only be confirmed by virological testing. For those older than 18 months, HIV infection can be confirmed by HIV antibody testing. ‡Applies only to discontinuation related to immune restoration on ART.

infections in high HIV-prevalence countries (with and without malaria). As microbial resistance increases, we will need to know whether other effective prophylactic regimens can be implemented and how this might be done on a large scale. Future scenario modelling and health economic assessments will be needed to gather this information.

Inadequate policy guidance on co-trimoxazole prophylaxis

The provision of HIV/AIDS care in the low-resource setting has mainly focused on antiretroviral drugs for treatment of HIV and for prevention of mother-to-child transmission (PMTCT) of HIV. Little or no consideration has been given to co-trimoxazole prophylaxis. ART provision has also focused mainly on adults, and since policy guidance on co-trimoxazole is usually integrated

within such guidelines, there is a resulting lack of guidance on co-trimoxazole prophylaxis for infants and children at the national level. Since 2006, WHO has begun to produce guidelines for use of co-trimoxazole and ART in infants and children.

Actions required

National policy guidelines on co-trimoxazole prophylaxis are required that explicitly separate adults and children. Panel 1 and panel 2 specify criteria for when to initiate and when to discontinue co-trimoxazole prophylaxis. Guidelines also need to clearly define doses for split-dose tablets and if available, syrups or soluble formulations (table). Training on co-trimoxazole prophylaxis for children and adults needs to be incorporated into the HIV/AIDS-related training curriculum taught to clinicians, nurses, and other care providers. The co-

	Recommended daily dose	Suspension (5 mL syrup; 200 mg/40 mg)	Paediatric tablet (100 mg/20 mg)	Single strength adult tablet (400 mg/80 mg)	Double strength adult tablet (800 mg/160 mg)
Less than 6 months	100 mg sulfamethoxazole/ 20mg trimethoprim	2.5 mL	One tablet	A quarter of a tablet, possibly mixed with feeding	NA
6 months to 5 years	200 mg sulfamethoxazole/ 40 mg trimethoprim	5 mL	Two tablets	Half a tablet	NA
6–14 years	400 mg sulfamethoxazole/ 80 mg trimethoprim	10 mL	Four tablets	One tablet	Half a tablet
15 years or more	800 mg sulfamethoxazole/ 160 mg trimethoprim	NA	NA	Two tablets	One tablet

NA= applicable. Doses of formulations shown as sulfamethoxazole/trimethoprim.

Table: Co-trimoxazole formulations and dosage for infants and children with HIV infection or exposed to HIV infection

trimoxazole policy should also be incorporated into guidelines and ongoing training involving integrated management of childhood illnesses (IMCI), PMTCT, tuberculosis, and HIV/AIDS care.

Limited identification and recruitment of HIV-exposed and HIV-infected children for co-trimoxazole

Opportunities for early identification of HIV-exposed children are limited for three main reasons. First, coverage of PMTCT programmes in countries with a high prevalence of HIV remains low,²⁹ meaning that most HIV-exposed infants are not being identified or are being lost from the health system.³⁴ Second, countries with a high burden of HIV have not maximised the opportunity of child-health programmes such as the Expanded Program of Immunisation (EPI) to identify HIV-exposed children. For example, in Swaziland where the antenatal HIV prevalence rate is particularly high (estimated to be 42%), about four out of every ten children attending EPI and child clinics could be considered HIV-exposed. Of these children, one to two are likely to be HIV-infected and could benefit from early HIV testing, co-trimoxazole, and ART. Finally, the high possibility of obtaining false-positive results from antibody-based rapid HIV tests in children under 18 months of age born to HIV-positive mothers in resource-limited settings makes it difficult to determine infection in HIV-exposed children. This problem is a major policy bottleneck for early administration of co-trimoxazole prophylaxis and ART,²⁴ since health systems in some countries are unwilling to provide co-trimoxazole to children unless HIV infection is confirmed. Furthermore, care providers at different levels of the health system have not been adequately trained to be able to maintain a high index of suspicion for recognition of signs and symptoms suggestive of HIV infection in children. Opportunities for active recruitment have also been grossly under-used or missed in voluntary counselling and HIV-testing sites, clinics for under-5-year-olds, the general out-patient department, and sites visited by people at high risk of HIV infection, such as tuberculosis clinics, paediatric wards, and paediatric nutritional rehabilitation units.

Actions required

Efforts should be made to rapidly accelerate the expansion of PMTCT services as an essential component of routine maternal and child-health services at all levels of the health system. This action would allow early detection of HIV-positive mothers and children eligible for both ART and co-trimoxazole prophylaxis. Advocacy for the development of specific, easy-to-use, and affordable HIV diagnostics for identifying HIV infection in children under 18 months of age is urgently required. At the moment, the only way of confirming HIV infection in this age-group is through virological antigen testing (eg, with PCR), which is only available in a few countries or at limited sites. In practice, this poses a practical dilemma to policymakers and clinicians in most countries, since it means one of two choices: (1) blanket administration of co-trimoxazole to all children under 18 months of age born to HIV-positive mothers in line with WHO/UNICEF recommendations, or (2) waiting until the HIV status is confirmed at 18 months, by which time infection-related mortality, including mortality caused by *P jirovecii* pneumonia, would have taken its toll on a large proportion of HIV-infected children.²³

Where PCR is available, efforts should be made to test the infant 6 weeks after cessation of breastfeeding to effectively target continuation of co-trimoxazole to only infants that have confirmed infection. In settings where PCR is not yet available, in light of high mortality, infants and children under the age of 18 months should be promptly offered co-trimoxazole and considered for ART on a presumptive basis until a definitive HIV diagnosis is made after 18 months.^{4,35} For countries where logistic and other operational constraints challenge the feasibility of offering co-trimoxazole to all HIV-exposed children under 18 months of age, a compromise strategy would be to offer co-trimoxazole to all children born to HIV-positive mothers from 4–6 weeks until 6 months of age, when the risk of *P jirovecii* pneumonia-related mortality is highest.²³

Clinicians, nurses, and care providers need training to recognise possible HIV-related clinical features in infants and young children at all sites where there is contact with children. In settings where HIV prevalence is high, such

as tuberculosis clinics and nutritional rehabilitation units, health-care workers should also be encouraged to routinely offer HIV testing.²⁸

Approach to HIV testing in pregnant women, symptomatic children, and at high-risk sites

HIV testing in pregnant women, symptomatic children, and at high-risk sites (ie, health-care facilities visited by people at high risk of HIV infection) have until now involved an “opt-in” approach that is client-initiated. HIV testing and case-finding was therefore passive and did not facilitate knowledge of HIV status.

Actions required

HIV testing in these three specific groups needs to move towards an “opt-out” or active approach that is health-provider initiated.³⁶ For pregnant women attending PMTCT programmes, HIV testing should be offered routinely as part of a standard screening package (provider-initiated testing and counselling [PITC]). Understandably, the barriers preventing the scale-up of HIV testing in pregnant women in different countries might be highly contextual and scalability, acceptance, and feasibility might vary. However, experience from Botswana^{37,38} and Zimbabwe³⁹ shows that introduction of a PITC approach in antenatal services with rapid, same-day results greatly increases uptake of HIV testing and the percentage of women receiving PMTCT interventions. These findings highlight the potential public-health impact of introducing PITC within programmes that attempt to increase the number of people with access to HIV prevention and treatment services. Thus, despite the myriad of potential logistic and social barriers to HIV testing that might exist in different contexts, introducing the PITC approach would be the first important step for increasing acceptance and knowledge of HIV status as well as uptake of PMTCT interventions. For infants and children who present with symptoms or signs that could be attributable to HIV infection, HIV testing should be routinely offered in an opt-out manner as part of the diagnostic work-up for patients and a basic standard of care (diagnostic HIV testing and counselling, DTC). High-risk sites such as tuberculosis clinics, paediatric wards, and nutritional rehabilitation units should be considered a priority for DTC because this will increase the chance of HIV case-finding in children. For example, a study in Botswana showed that 60% or more children admitted to paediatric wards in major hospitals were HIV-positive.⁴⁰ In such a country, moving to an active DTC strategy could increase the number of children identified as HIV-positive and improve their eventual outcomes in terms of morbidity and mortality.⁴⁰ HIV-testing guidelines need to include explicit guidance on PITC and DTC, and counsellors and care providers must be adequately trained.³⁵

Prescriptions of co-trimoxazole prophylaxis are restricted to isolated HIV/AIDS clinics

Although identification of HIV-exposed infants and HIV-infected children might occur at different sites in the health system, patients are often obliged to present themselves to specialised HIV/AIDS clinics, often located in hospital settings, if they are to receive a prescription of co-trimoxazole prophylaxis. This means additional waiting times in queues, the need for separate visits, or long distance travel to hospitals for monthly prescription refills. The latter is an important barrier for those committed to continuing prophylaxis; one of the main reasons for stopping prophylaxis is the high cost of transport to distant health facilities.⁴¹

It is much more convenient to provide a 3-month rather than 1-month supply of drugs when distance and transport costs are issues and this is likely to improve adherence.

Actions required

An integrated one-stop service that provides co-trimoxazole prescriptions at all sites where there is contact with children would foster a patient-friendly approach. In particular, children who are born to HIV-infected mothers or children identified as being HIV-positive through voluntary counselling and HIV-testing clinics, clinics for under 5-year-olds, the general outpatient department, tuberculosis clinics, or nutritional rehabilitation units should be given a prescription of co-trimoxazole (on site) for their mothers to take to the pharmacy for collection of the drugs provided there are no contraindications.

To improve access for continued co-trimoxazole prophylaxis, drug refills should be made readily available at decentralised sites including health centres and home-based care programmes. All health workers or members of multidisciplinary care teams should be able to prescribe co-trimoxazole.

Inadequate information, education, and communication advocating co-trimoxazole

Because of policymakers' concerns about effectiveness and development of drug resistance following widespread use of co-trimoxazole at country level, little or no emphasis had been placed on developing specific information, education, and communication messages advocating co-trimoxazole within health services or the community. Individuals that use health services might therefore be insufficiently aware of the benefits of co-trimoxazole prophylaxis.

Actions required

There is an urgent need to develop specific messages to increase awareness and the demand for co-trimoxazole both among health workers and in the community. Such messages should be simple and clear—for example, “taking your daily doses of co-trimoxazole could provide

you with protection from a number of common HIV-related illnesses including malaria and diarrhoea, considerably reducing your risk of death from HIV/AIDS, therefore providing you with benefits before starting ART and also while on ART”.

Motivational talks advocating the use of co-trimoxazole in the community and within different health services should be routinely done by a joint team of health workers and people living with HIV/AIDS.

Problems with co-trimoxazole drug supply and monitoring

Most national programmes do not have systems for accurately estimating programme needs or for monitoring consumption related to prophylaxis. Co-trimoxazole drug supplies provided to health facilities are used rather blindly for both treatment and prophylaxis. Co-trimoxazole stock shortage is therefore a common operational problem that directly hampers initiating and continuing prophylaxis. For example, in a recent national survey in Malawi at 94 public-health facilities providing ART, 55% of facilities were out of stock of co-trimoxazole at the time of the supervisory visit (HIV Unit, Ministry of Health, Malawi, unpublished data).

Actions required

An initial estimate of national requirement would need to be calculated to decide how much co-trimoxazole is required as a “kick-start” for central medical stores. The pharmacy in each health facility should centralise supplies of co-trimoxazole for patients and should keep a “vital register” of co-trimoxazole prophylaxis. Patients should be given a unique co-trimoxazole registration number and this number plus name, age, and sex should be listed on the register. The unique registration number will also be written on the patient card or health passport if this exists. Every time a patient is given co-trimoxazole, the date should be entered into the register. Therefore, the number of patients (adults and children) who start co-trimoxazole and the number who continue co-trimoxazole can be monitored by regular checks of the vital register. The use of such registers merits pilot testing and would certainly help with logistics of procurement and distribution.

Co-trimoxazole should be supplied through existing drug distribution systems and should be provided free of charge. Districts will need to ensure that a “budget line” is created for co-trimoxazole prophylaxis and that there is an uninterrupted supply of the drug for both treatment and prophylaxis. There will be a need to designate a responsible authority at national level who monitors the scale-up of co-trimoxazole prophylaxis.

Lack of implementation plans and targets for children

Few countries have so far drawn up phased implementation plans and a system for monitoring and reporting of progress.

Actions required

A phased plan for scale-up and integration of co-trimoxazole prophylaxis in children within existing child-care and HIV services, including specific population targets and indicators, should be developed. A minimum set of indicators could include: the existence of an effective national coordination mechanism; existence of a national policy on co-trimoxazole prophylaxis; a co-trimoxazole scale-up plan, with budgetary allocation; the proportion of HIV-exposed infants in PMTCT programmes who receive co-trimoxazole prophylaxis at 6–8 weeks; and the proportion of HIV-infected children within existing health services (including paediatric HIV care, IMCI, nutritional rehabilitation units, and home-based care) who access co-trimoxazole.

Although co-trimoxazole implementation could provide a useful and crucial entry point on which to build other interventions, by no means should it lead to the

Panel 3: Programmatic issues and logistic/operational considerations linked to implementing co-trimoxazole prophylaxis in children

Policy and programme implementation

- National guidelines on clinical care, ART, and PMTCT to include co-trimoxazole prophylaxis as a part of the basic care package
- Ensuring availability of appropriate doses and drug formulations for children
- Assessing legal and policy options to allow co-trimoxazole access at all sites that have contact with HIV-exposed and HIV-infected children
- Provision of co-trimoxazole free of charge to children
- Inclusion of co-trimoxazole for preventive HIV treatment in the essential drug kit

HIV testing

- Training of health providers in antenatal care, child-health programmes, tuberculosis clinics, paediatric wards, and nutritional rehabilitation units on the provider-initiated HIV testing and counselling (opt-out) approach
- Provision of infrastructure space and rapid test kits for HIV testing and counselling
- Increasing access to virological testing to aid early identification of HIV-infected children

Patient information

- Adapted information, education, and communication tools targeting health providers and patients to promote co-trimoxazole prophylaxis in children

Drug stocks and supplies

- Introducing co-trimoxazole vital registers to ease calculation of consumption and forecasts of drug needs
- Existing drug distribution systems to include integrated management of procurement and supply
- Ensuring uninterrupted drug supply for treatment and prophylaxis
- Specific budget allocation for co-trimoxazole

Monitoring and evaluation

- Regular reporting of uptake of co-trimoxazole within specific programmes and evaluation against set targets
- National surveillance of antimicrobial resistance of pneumonia, dysentery, and malaria in children

ART=antiretroviral therapy. PMTCT=prevention of mother-to-child transmission of HIV.

Search strategy and selection criteria

Data and information related to this Review were identified by searches of Medline, Google, and references from relevant articles. Search terms included "cotrimoxazole", "cotrimoxazole prophylaxis", "trimethoprim-sulphamethoxazole", "scaling-up", and "HIV in children". Only papers published in English language were reviewed. No date restrictions were set in these searches.

propagation of a vertical co-trimoxazole programme. What is needed is to link co-trimoxazole as an integral part of a standard package of care within PMTCT, ART, and other child-health programmes, including distribution of insecticide-treated bednets for malaria prevention and safe-water vessels.

Programmatic issues and logistic/operational considerations

The main programmatic issues and actions required regarding the logistic and operational aspects linked to offering co-trimoxazole prophylaxis in children are highlighted in panel 3.

Funding gaps in high HIV-prevalence settings

Although co-trimoxazole is cheap, large-scale implementation of co-trimoxazole prophylaxis in settings with a high prevalence of HIV will need substantial resources and logistics. With a conservative global estimate of 2.8 million children requiring co-trimoxazole in 2005 (2.3 million HIV-infected children and 530 000 new HIV infections),¹ this would amount to US\$8.5–23 million per year on drug costs only, using an estimated annual cost of \$3–8 per child.

Actions required

Development partners and donor countries should support widespread implementation of co-trimoxazole prophylaxis and ensure that co-trimoxazole is included as a specific component in funding proposals. Co-trimoxazole for HIV-exposed and HIV-infected children should be considered a priority intervention that is included in scale-up of paediatric HIV care and treatment.

Conclusions

There are considerable clinical and operational benefits of offering co-trimoxazole prophylaxis to children in countries with a high prevalence of HIV. Serious efforts need to be made to scale-up this widely available and easy-to-use medication.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

The initial draft of this document was prepared for a technical consultation of the Global Partners Forum on Children Affected by HIV and AIDS under the aegis of UNICEF, UNAIDS, UK Department for

International Development, and the UK Consortium on AIDS and International Development. We thank various individuals from these organisations for their useful comments on the initial draft paper. We are also very grateful to Pierre Humblet (Médecins Sans Frontières, Brussels, Belgium) for his useful comments on operational issues.

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