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Reconsidering empirical cotrimoxazole prophylaxis for infants exposed to HIV infection

Christopher J. Gill,[1] Lora L. Sabin,[1] Joseph Tham,[2] & Davidson H. Hamer[3]

Abstract Infants with HIV infection are vulnerable to *Pneumocystis carinii* pneumonia (PCP) during their first year of life. WHO and the Joint United Nations Programme on HIV/AIDS now recommend that all children of HIV-positive mothers receive prophylactic cotrimoxazole against PCP from six weeks of age and continue this therapy until exposure through breast milk ceases and the infant is confirmed to be HIV-negative (rarely before one year of age). Empirical prophylaxis invokes a trade-off between possible benefit to the infant versus the risk of resistance to antibiotics and antimalarials. From a critical analysis of the literature, we offer a conceptual model demonstrating how, under certain circumstances, a policy of mass cotrimoxazole prophylaxis may be counterproductive.

Keywords Trimethoprim-sulfamethoxazole combination/therapeutic use/adverse effects; Pneumonia, Pneumocystis/drug therapy; HIV infections/complications; AIDS-related opportunistic infections/drug therapy; Disease transmission, Vertical; Drug resistance, Microbial; Sulfadoxine/pharmacology; Pyrimethamine/pharmacology; Infant; Risk assessment; Meta-analysis; Models, Theoretical; Africa (*source: MeSH, NLM*).

Mots clés Triméthoprime-sulfaméthoxazole, Association/usage thérapeutique/effets indésirables; Pneumocystose/chimiothérapie; HIV, Infection/complications; Infections opportunistes liées SIDA/chimiothérapie; Transmission verticale maladie; Résistance microbienne aux médicaments; Sulfadoxine/pharmacologie; Pyriméthamine/pharmacologie; Nourrisson; Evaluation risque; Méta-analyse; Modèle théorique; Afrique (*source: MeSH, INSERM*).

Palabras clave Combinación trimetoprim-sulfametoxazol/uso terapéutico/efectos adversos; Neumonía por Pneumocystis carinii/quimioterapia; Infecciones por VIH/complicaciones; Infecciones oportunistas relacionadas con el SIDA/quimioterapia; Transmisión vertical de enfermedad; Resistencia microbiana a las drogas; Sulfadoxina/farmacología; Pirimetamina/farmacología; Lactante; Medición de riesgo; Meta-análisis; Modelos teóricos; África (*fuente: DeCS, BIREME*).

Arabic

Voir page 295 le résumé en français. En la página 295 figura un resumen en español.

Introduction

In 2000, WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) issued a provisional recommendation: all African infants born to mothers infected with human immunodeficiency virus (HIV) should receive empirical cotrimoxazole (trimethoprim–sulfamethoxazole) prophylaxis against *Pneumocystis carinii* (now called *Pneumocystis jiroveci*[a]) pneumonia (PCP) from six weeks of age (*1*). This proposal was made for the following reasons: the high number of deaths from PCP in infants with HIV infection; cotrimoxazole's efficacy for preventing PCP in adults; and the difficulty in determining HIV infection in exposed infants in poor countries. Nevertheless, cotrimoxazole prophylaxis based solely on HIV exposure, without confirmation of HIV infection status within the first month of life, is not the way this drug is usually used in developed countries and may have unforeseen consequences.

In developed countries, cotrimoxazole prophylaxis for infants exposed to HIV is also recommended from six weeks of age but usually discontinued once HIV infection has been excluded using a direct viral detection assay — ideally within the first few months of life. Direct viral assays are expensive, however, forcing poorer nations to rely on antibody-based HIV tests. Antibody assays are useful for diagnosing HIV in adults or older children but less reliable for neonates or infants. Persistence of maternal HIV antibodies gives high numbers of

false positives until at least 12 months of age (*2*). Moreover, in countries where safe, culturally acceptable, feasible, affordable and sustainable alternatives to breastfeeding are lacking, up to 40% of infant HIV infections occur via breastfeeding (*3*). Because breastfeeding is nearly universal in developing countries, even tests that directly test for the presence of HIV rather than serologic responses would not resolve this dilemma unless applied after the child has been weaned. In this context, a negative viral assay would not alter the indication of cotrimoxazole until the child is no longer at risk of acquiring HIV through breast milk. Hence, infants exposed to HIV would continue prophylaxis until both weaned and shown to be antibody negative — conditions rarely satisfied before one year of age.

Between 600 000 and 800 000 infants with HIV infection are born each year, 90% of them in sub-Saharan Africa (*4*). This however represents only 13–30% of infants with peripartum HIV exposure (*3*). Consequently, at least 2 million infants annually would need prophylaxis under WHO/UNAIDS guidelines. Even though cotrimoxazole is inexpensive on a per-dose basis, providing so many children with a year's supply poses formidable financial and logistical challenges for Africa's poorest nations. Even assuming these challenges could be overcome, it remains unproven whether the potential benefits would exceed the potential risks of mass prophylaxis.

To explore these issues, we critically analyse the natural history of HIV and PCP in African infants, the evidence for cotrimoxazole's benefit in this group, and the known and theoretical risks of prophylaxis. From this analysis, we offer a theoretical model contrasting the risks and benefits of prophylaxis as an aid to framing future public policy responses to the problem of PCP in infants with HIV infection, and for defining future research priorities.

Natural history of HIV and PCP in young children

HIV infection proceeds more rapidly to AIDS in infants than adults. AIDS-related deaths peak during the first six months of life, followed by a more gradual progression to AIDS in the survivors (*5*). Natural history studies from Europe and the USA before the era of highly active antiretroviral therapy (HAART) are illustrative. Twenty six per cent of infected children developed clinical AIDS before reaching 12 months and 17% died (*6*); median survival was 38 months (*7*). Mortality rates in African infants are even higher. In Rwanda, mortality was 45% and 62% by age 2 years and 5 years, respectively (*8*). Of Malawian infants surviving their first year, 30% died by age 2 years and another 45% died by age 3 years (*9*). Overall, 90% of HIV-infected African children die before age 5 years (*10*).

In the pre-HAART era, HIV-infected infants in developed countries frequently died from PCP, particularly during their first six months of life (*11*) — a trend central to current prophylaxis guidelines. In African infants, the proportion of mortality caused by PCP versus other infectious diseases is unknown but probably small compared with the estimated annual 6 million deaths from malaria, diarrhoeal disease, and bacterial pneumonia (*12*). Autopsies and studies of African children infected with HIV and hospitalized for severe pneumonia demonstrate the importance of PCP (Table 1) but fail to indicate the proportion of all HIV-infected African infants who succumb to PCP compared with other causes. Natural history studies would provide these data but to date none of the prospective African trials have included PCP incidence data. In the absence of these data, we are forced to extrapolate the incidence data using pre-HAART studies from the USA, where first-year PCP incidence has been reported to range between 12.8% and 25% (*7, 13*). Based on these data, a plausible estimate of the annual incidence of infant PCP in Africa is between 76 000 (0.128 x 600 000) and 200 000 (0.25 x 800 000) cases.

Will cotrimoxazole prevent PCP in African children?

The survival benefit of cotrimoxazole is well established for adults with HIV infection living in developed countries but less well known for Africa (*14*). Only three randomized trials have studied primary prophylaxis with cotrimoxazole in Africa. The first was conducted among a population of adults with HIV infection receiving treatment for TB in Abidjan, Côte d'Ivoire. In this cohort, cotrimoxazole reduced all-cause mortality by 46% and hospitalizations by 43% compared with placebo (*15*). Cotrimoxazole users had reduced rates of enteritis (1.1% vs 3%, $P = 0.04$), bacteraemia (0.5% vs 3%, $P = 0.01$), and mycobacterial disease (3.9% vs 6.4%, $P = 0.14$) (*15*). The second study, also from Abidjan, was not limited to HIV patients with TB. Here, fewer patients receiving cotrimoxazole were hospitalized for pneumonia (0.7% vs 7%, $P < 0.001$), malaria (1% vs 9.6%, $P < 0.01$), or isosporiasis (0.7% vs 4%, $P = 0.02$). Prophylaxis had no significant impact on mortality (8.4% vs 9.2%, $P = 0.5$), but did cause increased rates of unexplained fever (13.6% vs 10%, $P < 0.01$) (*16*). While insufficiently powered to detect a mortality difference, the Kaplan–Meier curve provides little optimism that a clinically meaningful benefit was missed. The third study, from Dakar, Senegal, found no impact on either mortality or hospitalization, but was ultimately inconclusive, having been terminated early following the publication of the Abidjan studies (*17*).

While sought, PCP was not detected in either Abidjan study. This finding reinforces an emerging view that PCP may be a less important opportunistic pathogen for African adults with AIDS, compared with adults in developed nations. One possible explanation is that Africans with HIV succumb to TB or other infectious diseases long before their CD4 counts drop to a level where PCP becomes a realistic threat. If so, cotrimoxazole's main benefit for African adults may lie in preventing common bacterial and parasitic diseases.

The WHO/UNAIDS guidelines — including the recommendation for empiric cotrimoxazole for infants — emerged shortly after the publication of the Abidjan studies. This is remarkable given that neither study provided any information about the optimal use or efficacy of cotrimoxazole in children. While the evidence for PCP's importance in African children with HIV infection is robust (Table 1), evidence for cotrimoxazole's efficacy in this age group is weak. To date, no randomized trials of cotrimoxazole's efficacy have been conducted. Evidence supporting the use of cotrimoxazole in children with HIV infection rests principally on observational studies from the USA (*18*). Studies from developing countries consist of an ecological study from Thailand that documented a rise in community cotrimoxazole use over a period when PCP hospitalizations in children declined (*19*), and two retrospective analyses showing a reduced proportion of PCP in African infants with HIV infection and pneumonia among those using prophylaxis before hospitalization (*20, 21*). A third case–control study, however, found no reduction in PCP rates due to prophylaxis (*22*). One concern with this study's conclusion arises from the fact that cases were

Table 1. *Pneumocystis carinii* pneumonia studies in HIV-infected African children

Study site	Year	Cohort description	No.of patients with PCP	Age of PCP cases	Other infections	Reference
Autopsy studies						
Côte d'Ivoire	1996	Hospitalized infants, all causes of death evaluated	11 (10)[a, b]	All <14 months	8 of 14 children aged >14 months had measles pneumonia	45
Zimbabwe	1997	Infants dying at home	19 (15.5)	Range: 1–7 months	7 of 19 had CMV	46
South Africa	1996	ICU patients with severe pneumonia	14 (77.8)[c]	Mean: 4 months	14 of 18 had CMV	47
Zimbabwe	2001	Hospitalized infants dying of pneumonia	16 (67)	All were "infants"	2 of 16 had CMV	48
Zambia	2002	Hospitalized children dying of pneumonia	58 (32)	0–5 months: 45 cases; 6–11 months: 6 cases; 1–16 years: 7 cases	54 of 264 had TB 43 of 264 had CMV	49
Botswana	2003	Hospitalized infants, all causes of death evaluated	10 (28.6)	< 7 months	4 of 35 died of TB; 3 of 35 died of CMV	50
Clinical outcome studies						
Malawi	1997	Children with severe pneumonia	5 (8)	3–6 months: 4 12 months: 1		51
Malawi	2000	Children with severe pneumonia	16 (10.6)	Range: 2–5 months		52
South Africa	2000	Children with severe pneumonia	15 (9.9)	Median: 3 months		20
South Africa	2002	Children with severe pneumonia	51 (48.5)	Median: 4 months		21
South Africa	2002	Children with severe pneumonia	101 (43.7)[d]	Median age 4 months		22

[a] Figures in parentheses are percentages.
[b] 33% of HIV-positive infants aged 1–14 months died of PCP; no cases occurred in older infants.
[c] Only 18/36 patients were tested for PCP.
[d] Proportion of PCP of all episodes of pneumonia. Excluding children with multiple episodes of PCP, PCP accounted for 52.4% of all severe pneumonias.
   CMV = cytomegalovirus; ICU = intensive care unit; PCP = *Pneumocystis carinii* pneumonia; TB = tuberculosis.

defined as children with HIV infection and confirmed PCP, and therefore may have included many children who had simply failed prophylaxis. It is unclear whether or not these children are representative of all children with HIV infection. Nor is it possible to infer how many children receiving prophylaxis remained well and avoided hospitalization.

Despite these ambiguities, the protective benefit found in studies from the USA establishes a strong moral imperative to provide cotrimoxazole to African infants either known or clinically suspected to have HIV infection — in the absence of data demonstrating its ineffectiveness or harm. Accepting the likelihood that prophylaxis will reduce PCP incidence in African infants with HIV infection does not mean that the benefits of mass prophylaxis will outweigh its risks when applied empirically to a population in which children infected with HIV will be a minority.

What are the risks of cotrimoxazole prophylaxis?

Rash, fever, and anaemia are all common during cotrimoxazole prophylaxis (23), and particularly in people with HIV infection (24). Cotrimoxazole appears better tolerated in children (25). Rare life-threatening side-effects, including severe hepatitis or Stevens–Johnson syndrome, can also occur though their incidence is difficult to predict from small clinical studies.

Antimicrobial resistance is arguably the most important adverse consequence of prophylaxis. Children taking antibiotics for a variety of chronic conditions — sickle-cell anaemia, recurrent urinary tract infections, and chronic otitis media — quickly become colonized with drug-resistant bacteria (26–28). Adults with HIV infection taking prophylactic cotrimoxazole also experience drug resistance (29). The list of pathogens whose epidemiology could be altered by cotrimoxazole exposure includes *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, enteropathogens (*Shigella* spp., *Salmonella* spp., *Isospora belli*), and *Neisseria* spp.

Resistant pathogens spread readily from infants to close contacts (30, 31), thereby extending this consequence of prophylaxis to families and ultimately the community at large. Rising cotrimoxazole resistance rates could impair the effectiveness of the WHO's Integrated Management of Childhood Infections (IMCI) guidelines, which currently recommend cotrimoxazole as first-line therapy for a variety of childhood infections (32).

The genetics of drug resistance adds another layer of complexity. Transmissible genetic elements often incorporate

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multiple antibiotic-resistance genes. For example, prior cotrimoxazole use has been identified as a risk factor for colonization with penicillin resistant pneumococci (*33*). Thus, our mental calculus of cotrimoxazole's impact extends beyond cotrimoxazole resistance alone, to include also penicillins, cephalosporins, macrolides, tetracyclines, and chloramphenicol (*28, 34, 35*).

Widespread cotrimoxazole use could also foster sulfadoxine–pyrimethamine resistance in *Plasmodium falciparum*, an organism which kills approximately one million children each year — the most attributable to any single childhood pathogen (*36*). With the loss of chloroquine as a reliable treatment for malaria, sulfadoxine–pyrimethamine has emerged as the first-line antimalarial throughout Africa. Rising resistance rates meant it was abandoned in the Amazon region of Brazil within a decade of introduction (*37*), and sulfadoxine–pyrimethamine may be a temporary solution to the problem of chloroquine resistance in Africa as well. Inexpensive and non-toxic alternatives are currently lacking, making it essential to maximize sulfadoxine–pyrimethamine's useful life (*38*).

Cotrimoxazole and sulfadoxine–pyrimethamine are close pharmacologically and share extensive in vitro cross-resistance (*39, 40*). Indeed, while cotrimoxazole is not typically considered an antimalarial, comparative studies show it to be equally effective as sulfadoxine–pyrimethamine for treating falciparum malaria (*41, 42*). As yet, there is no convincing evidence that this in vitro cross-tolerance will translate into clinical failures, though interestingly, sulfadoxine–pyrimethamine has been linked with increased rates of cotrimoxazole-resistant pneumococci (*43*). But this is not reassuring given the absence of prospective studies addressing the question. With the stakes that are involved, it would be irresponsible not to question whether the efficacy of sulfadoxine–pyrimethamine, and potentially other sulfonamide-containing antimalarials, could be reduced by mass cotrimoxazole prophylaxis.

Another concern is whether cotrimoxazole prophylaxis could impede the acquisition of natural malaria immunity by infants. Because of maternal antibodies, infants in areas of high malaria incidence are often born with immunity to malaria (*44*). As this passive immunity wanes, natural immunity emerges after exposure to infectious mosquitoes. Cotrimoxazole reduces both clinical malaria and asymptomatic parasitaemia and, in so doing, could hypothetically attenuate the normal acquisition of immunity. This creates an ethical dilemma since HIV-exposed infants discontinuing prophylaxis, after a negative HIV test at one year of age, might be more vulnerable to severe malaria than if they had never received prophylaxis.

Do the benefits exceed the risks of empiric prophylaxis?

Table 2 summarizes some of the most important risks and benefits of prophylaxis. Though their magnitudes are unknown, conceptualizing their interactions may still allow us to derive insights into how these risks and benefits compete, and identify areas where additional data could support a formal quantitative analysis.

Fig. 1 presents a basic conceptual model of the relationship between the risks and benefits of mass empiric prophylaxis when applied to a mixed population of HIV-positive and HIV-negative children. For simplicity we consider both risks and benefits to exist on a universal scale, such that 1 risk unit is equivalent in magnitude to 1 benefit unit. Because prophylaxis chiefly aims to prevent PCP, the benefit of empiric prophylaxis increases in proportion to HIV's prevalence in the target population (if prevalence were 100%, benefits would be maximal). Setting aside the less worrisome risk of cotrimoxazole side-effects, there is no compelling reason to expect that the more important risks of prophylaxis (microbial resistance) will be influenced by

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Table 2. **Known and theoretical benefits and risks of cotrimoxazole prophylaxis**

Potential benefits of cotrimoxazole	Who experiences this benefit?	Timing of effect	Effect of time on magnitude of benefit
• Prevents PCP	HIV-infected infants	Immediate	Declines as antibiotic resistance rises
• Prevents other opportunistic parasites: toxoplasmosis, isosporiasis	HIV-infected infants	Immediate	Declines as parasites acquire resistance
• Prevents bacterial infections	HIV-infected infants	Immediate	Declines as bacteria acquire resistance
• Prevents malaria	HIV-infected and uninfected infants	Immediate	Declines as *Plasmodia* acquire resistance
Potential risks of cotrimoxazole	**Who experiences this risk?**	**Timing of effect**	**Effect of time on magnitude of risk**
• Financial cost of purchasing drugs and of infrastructure to provide drugs	Society at large; guardians of infants (if paying out of pocket)	Immediate	Remains constant
• Toxicities associated with cotrimoxazole use	HIV-infected and uninfected infants	Immediate	Remains constant
• Higher rates of cotrimoxazole-resistant, and multidrug-resistant bacteria	HIV-infected and uninfected infants, community at large	Delayed	Increases as cotrimoxazole resistance increases
• Increased rates of SP-resistant malaria, SP treatment failures and malaria mortality	HIV-infected and uninfected infants, the community at large	Delayed	Increases as SP resistance increases
• Impaired acquisition of natural immunity to malaria	HIV-infected and uninfected infants	Delayed	Declines as SP resistance increases

PCP = *Pneumocystis carinii* pneumonia; HIV = human immunodeficiency virus; SP = sulfadoxine–pyrimethamine.

Fig. 1. **Contrasting the benefits and risks of empiric cotrimoxazole for HIV-exposed infants.** This figure describes a conceptual model that contrasts the magnitude of the risks and benefits of mass empiric cotrimoxazole prophylaxis for HIV-exposed infants as a function of the HIV seroprevalence in the target population. The intersection point between the two lines indicates the point at which the aggregate risks and benefits of this strategy balance precisely; empiric prophylaxis is justifiable at higher levels of HIV prevalence, and unjustifiable at lower levels of prevalence
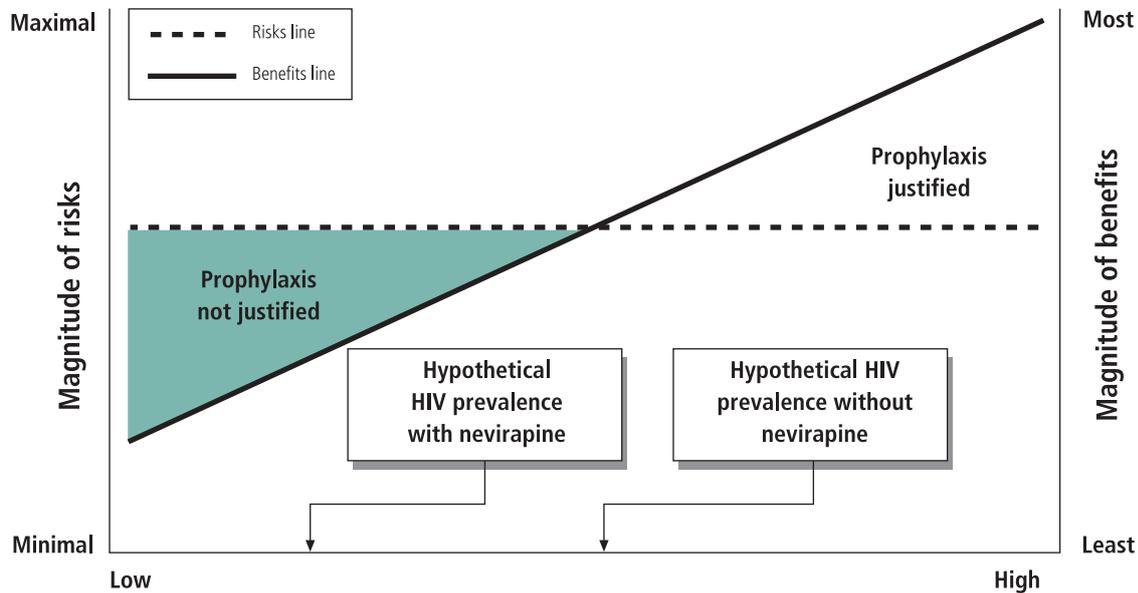
HIV infection per se. Therefore, the risk line should remain constant regardless of HIV prevalence. At some degree of HIV prevalence, the benefits and risks lines intersect and balance. When HIV prevalence exceeds this point, empiric prophylaxis is warranted; below this prevalence level, mass empiric prophylaxis is unjustified since the risks exceed benefits.

Our goal is to reduce PCP — and increase longevity — in HIV-positive children. Applying our current diagnostic limitations we do not know which HIV-exposed children are born infected or which will become infected during their first year. We will assume that the mother's HIV status will be ascertained during antenatal clinic voluntary counselling and testing (though in reality, this number will be reduced by those women who choose not to learn their HIV status). Currently, our options for preventing PCP in these children are either to use 4 million doses of nevirapine (half to the 2 million HIV-exposed infants and half to their HIV-positive mothers) or 750 million doses of cotrimoxazole to treat these children for one year each (2 million children exposed to HIV x 365 daily doses). Obviously, these are not mutually exclusive, and would probably be combined in the real world. This is logically appealing: nevirapine reduces the risk of HIV infection — and indirectly also PCP — in the majority, while cotrimoxazole protects the unlucky HIV-positive minority directly from PCP.

Careful examination of Fig. 1 reveals why this combined approach could have a paradoxical adverse effect. Let us assume that, in the absence of any intervention, this population's HIV prevalence places us precisely where the lines of risk and benefit intersect. If this population of HIV-exposed children receives nevirapine at birth, HIV prevalence will decline, shifting us to the left on the *x* axis. Even though nevirapine reduces the number of children at risk of PCP our ignorance of which children still become infected with HIV still compels us to provide cotrimoxazole presumptively to all 2 million. The result: even though cotrimoxazole's efficacy for preventing PCP for an

individual HIV-positive infant remains constant, at a population level the effectiveness of mass prophylaxis deteriorates and the strategy becomes unjustifiable because the risks now exceed the benefits.

The purpose of this subjective exercise is not to suggest that this scenario would necessarily be the result of mass prophylaxis. Indeed our current knowledge of the magnitude of the risks involved is simply inadequate to know at what HIV prevalence the risk and benefits lines intersect (or even if these theoretical lines are straight or curved). But this is precisely the point — we don't know where this critical threshold lies, so why is it acceptable to assume that we are safely above it?

Without providing a quantitative measure of these outcomes, our thought experiment still identifies two problems deriving from our ignorance of which children are actually HIV-positive. First, because the same number of cotrimoxazole doses are used to prevent fewer cases of PCP, nevirapine reduces the additional benefit of cotrimoxazole prophylaxis. Second, the prior use of nevirapine increases the ratio of risk to benefit of subsequent cotrimoxazole prophylaxis. Accordingly, we suggest that improving strategies for preventing postnatal HIV transmission and for identifying HIV-infected children earlier (so that cotrimoxazole prophylaxis can be appropriately applied to those who will benefit most) may prove a better investment of limited resources than mass empiric prophylaxis.

Conclusion

Ultimately, the merit of a mass empiric prophylaxis strategy rests on the degree of risk it entails. Mass prophylaxis will inevitably increase rates of drug-resistant bacteria and malaria in cotrimoxazole users — and likely their communities at large — but how quickly, and to what extent? Quantifying the magnitude of this risk is essential and we urge countries that choose to implement WHO's strategy to initiate their programmes

in parallel with a systematic means for prospectively monitoring the microbiological effects of mass prophylaxis in their populations. Given their unambiguous contribution to paediatric disease, monitoring the resistance patterns of *S. pneumoniae* and *P. falciparum* longitudinally would seem a logical starting point.

In their original declaration, WHO/UNAIDS acknowledged their strategy's potential for risk, but concluded that action was preferable to further debate (*1*). This sentiment is quite understandable given the magnitude of the humanitarian disaster unfolding before us. However, without a safety net of surveillance, it is critical that we better understand the consequences of this strategy, rather than taking a leap of faith. ■

Résumé

Remise en question du traitement préventif empirique par le cotrimoxazole chez les nourrissons exposés à l'infection par le VIH

Les nourrissons atteints d'infection par le VIH sont sensibles à la pneumocystose (pneumonie à *Pneumocystis carinii*) jusqu'à l'âge d'un an. L'OMS et le Programme commun des Nations Unies sur le VIH/SIDA recommandent actuellement d'administrer à tous les enfants nés de mère VIH-positive un traitement préventif par le cotrimoxazole contre la pneumocystose dès l'âge de six semaines et jusqu'à arrêt de l'exposition via le lait maternel et confirmation de la séronégativité de l'enfant vis-à-vis du VIH (rarement avant l'âge d'un an). Le traitement préventif empirique représente un compromis entre les avantages potentiels pour le nourrisson et le risque de résistance aux antibiotiques et aux antipaludiques. D'après une analyse critique des observations publiées, nous présentons un modèle théorique montrant comment, dans certaines circonstances, une politique de traitement préventif de masse par le cotrimoxazole peut être contre-productive.

Resumen

Reconsideración de la profilaxis empírica con trimetoprim y sulfametoxazol en lactantes expuestos a la infección por VIH

Los lactantes infectados por el VIH son vulnerables a la neumonía por *Pneumocystis carinii* (NPC) durante el primer año de vida. En la actualidad, la OMS y el Programa Conjunto de las Naciones Unidas sobre el VIH/SIDA recomiendan que todos los niños cuyas madres son VIH-positivas reciban profilaxis con trimetoprim y sulfametoxazol contra la NPC desde las seis semanas de vida, y que sigan con este tratamiento hasta que cese la exposición a través de la leche materna y se confirme que el niño es VIH-negativo (raramente antes del año de vida). La profilaxis empírica se fundamenta en un equilibrio entre el posible beneficio para el lactante y el riesgo de resistencia a los antibióticos y los antimaláricos. Basándonos en un análisis crítico de la literatura médica, proponemos un modelo conceptual que demuestra que, en determinadas circunstancias, una política de profilaxis masiva con trimetoprim y sulfametoxazol puede ser contraproducente.

Arabic

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Commentary

Cotrimoxazole prophylaxis for infants exposed to HIV infection

Stephen M. Graham[1]

Uncertainty remains about the risks and benefits of implementing guidelines on the use of cotrimoxazole prophylaxis for prevention of HIV-related infections in Africa (*1*). Gill et al. focus on recommendations for prophylaxis made by the World Health Organization and the United Nations Programme on HIV/AIDS (UNAIDS) for infants born to mothers with HIV infection, most of whom will not have HIV infection. They examine evidence of benefit, highlight concerns about risk, and propose a model that might be helpful in determining policy in various circumstances. A useful approach in principle but — as the authors conclude — important data required for this model remain unavailable, most notably for the magnitude of risk. Other issues, such as national policies and priority setting also need to be considered further.

Benefits

Around one-third of African infants with HIV infection die in the first year of life and *Pneumocystis carinii* (now called *Pneumocystis jiroveci*) pnemounia (PCP) is responsible for 30%-50% of deaths (*2,3*). This is the rationale for cotrimoxazole prophylaxis. Evidence of efficacy from controlled trials may not be available but such studies would be difficult to justify in this setting. Experience has shown that the introduction of routine cotrimoxazole prophylaxis for infants of HIV-infected mothers has markedly reduced the incidence of hospitalization and death caused by PCP (*3*).

Cotrimoxazole prophylaxis may also prevent illnesses in addition to PCP, particularly bacterial disease and malaria, with potential benefit to uninfected infants as well infants with HIV infection (*4,5*). In developing countries, incidence and case-fatality rate of bacterial pneumonia is high in infants, and passive immunity against pneumococcus may be less in children of mothers with HIV infection (*6,7,8*). Infants become more susceptible to severe malaria (with anaemia) around 4-6 months, when maternal passive immunity wanes.

Studies of cotrimoxazole prophylaxis in African adults, and a recent study of Zambian children aged 1-14 years, have shown improved survival in people with HIV infection (*4,5,9*). This benefit was not from prevention of PCP, which was rare, but from prevention of bacterial disease and malaria. The degree of protection, however, was variable between study groups and diseases. There have been no studies in infants of mothers with HIV infection.

The potential of preventing PCP will encourage mothers to overcome some of their reluctance to discover their HIV status, preferably as one element of a package of measures that includes prevention of mother-to-child transmission, and improved maternal care. Maternal death, we know, is a major risk factor for early death in infants of mothers with HIV infection (*2*).

[1] Clinical Research Fellow, Malawi-Liverpool-Wellcome Trust Clinical Research Programme and Department of Paediatrics, College of Medicine University of Malawi, Malawi (sgraham@mlw.medcol.mw). Tel: 265-1-676444; Fax: 265-1-675774.
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Risks

The risk of toxicity from cotrimoxazole is negligible (*9,10*). Gill et al. outline the major potential risk of widespread cotrimoxazole prophylaxis: increasing antimicrobial resistance of common pathogens such as *Streptococcus pneumoniae* and of *Plasmodium falciparum*. There is a consequent risk to individuals receiving cotrimoxazole, who may be more vulnerable to resistant pathogens, and to public health more broadly through shortening the useful life span of current therapies. Data to help determine the magnitude of these risks, in different settings of background resistance, are critical.

An additional risk in low-resource countries is that translating this policy into practice may hamper or dilute the effectiveness of other programmes. A number of health care strategies are rolled out at any one time, and these must be prioritized to avoid over-burdening the health system, especially because of the human resource crisis in many African countries with HIV endemics. From a child health perspective, prolonging the survival of a child with HIV infection may not have the same priority as improving maternal health or preventing mother-to-child transmission with antiretroviral therapy. Another priority may be preventing malaria by distributing insecticide-treated bed-nets. Whatever the choice, decisions to adopt global policy are best made at national level.

Improved diagnosis of HIV infection

Gill et al. highlight how the balance between risk and benefit will be altered by substantial reductions in rates of mother-to-child transmission. They also justifiably argue that improved diagnosis of HIV infection in infants should reduce duration of prophylaxis. This would, however, also depend on a policy — that may not be desirable — of bottle-feeding infants exposed to HIV infection to avoid late post-natal infection. There is evidence that, in the African context, maternal HIV antibodies do not persist in infants for as long as elsewhere which means that an HIV antibody test could be highly specific for infection as early as 6 months (*11*). Analyses of data from past cohort studies of African infants exposed to maternal HIV infection might help answer this question.

The way forward

Recognizing that PCP is a common but preventable cause of high mortality in African infants with HIV infection, an alternative strategy of cotrimoxazole prophylaxis until 6 months of age could prevent most cases of PCP while reducing the duration of prophylaxis and risk of antimicrobial resistance (*12*). Randomized-controlled trials of cotrimoxazole prophylaxis are difficult, but studies must be done that provide important data on risk in a number of settings with variable background resistance and HIV prevalence. Comparisons could be made between infants who are HIV negative (and receiving cotrimoxazole prophylaxis) but whose mothers are HIV positive and infants of who are HIV negative and whose mothers are HIV negative. Cost-effectiveness studies are required as well to evaluate a package of care that also includes antenatal testing, perinatal antiretroviral therapy, and care for the mother. ■

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