short-course prophylactic zinc supplementation in reducing the burden of ALRI among infants during the subsequent months. Furthermore, the magnitude and directionality of the effects estimated by this study bolster the conclusions of a previous meta-analysis, which reported no difference between the effects of short-course and routine zinc supplementation trials [9]. Future studies should assess the effectiveness of delivering prophylactic zinc supplementation at-scale, comparing the feasibility and cost-benefit of short-course and continuous regimens.

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Zinc for Prevention of Acute Respiratory Infections in Infants – Research Needs

Indian Perspective

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Pneumonia is responsible for 18% of under-five mortality as a result of an estimated 151 million new episodes each year occurring mostly in the marginalized and malnourished children in the developing countries who are often zinc-deficient [1]. In fact, the extent of zinc deficiency in a population is often estimated by the prevalence of stunting among these settings [2]. Zinc affects both non-specific and specific immune function at a variety of levels. In terms of nonspecific immunity, zinc affects the integrity of epithelial barrier, and function of neutrophils, natural killer cells, monocytes and macrophages [3,4]. Therefore, zinc conceptually promises to offer a beneficial impact on prevention, control and treatment of infections. Based on evidence from several randomized controlled trials and meta-analyses the World Health Organization (WHO) and the United Nations Children’s Fund recommended zinc supplementation for up to 2 weeks for management of acute diarrhea [5]. Similarly, several studies evaluated the effect of zinc supplementation in reducing the frequency and severity of respiratory infections children. Variable results have been reported from a series of meta-analyses that evaluated the role of zinc in prevention of pneumonia. Two meta-analyses in 1999 and 2007 reported a beneficial effect in preventing pneumonia in children [6,7]. Subsequently, in 2008, Roth, et al. [8] evaluated the
burden of ALRI attributed to zinc deficiency and concluded that zinc supplementation to young children prevented about one-quarter of ALRI cases, which could translate into reduction in infant mortality. Another meta-analysis of ten studies [9] concluded a reduction in incidence of ALRI defined by a specific definition but no effect on ALRI based on caregiver report. This finding was supported by a Cochrane review of studies in 2010 [10] but mitigated in the same year by another review which included eleven studies with robust methodology and consistent definition of pneumonia [11].

In this issue, Malik, et al. [12], reported a double blind randomized controlled trial to evaluate whether zinc prophylaxis for a short duration had any role in reducing the morbidity due to ARI in 272 apparently healthy infants of 6-11 months of age from two urban resettlement communities in Delhi, India. Nearly 40% of the population were wasted or stunted, more so in the placebo group. They reported an overall absence of effect on the incidence of acute respiratory infections (ARIs). There was a differential impact on acute upper respiratory infections (AURI) and acute lower respiratory tract infection (ALRTI). A slight but insignificant increase in incidence of AURTI but a reduction in incidence of ALRTI by 62% was observed. These results need to be interpreted with caution. The sample size was powered to observe a 20% reduction in an overall estimated ARI episodes of 5.5 episodes per child-year. The observed AURI and ALRTI episodes in the study were a mean of 7.2 and 1 per child-year respectively. So this study is largely underpowered to observe a difference in ALRTI. A significant decrease of 15% in days of ARI and 12% in duration of an episode of ARI were perhaps contributed largely by upper respiratory tract episodes which were 7 times more frequent than ALRTI.

The reported efficacy of zinc therapy for pneumonia, although encouraging, needs to be considered in the light of several caveats. Previously conducted meta-analyses report significant heterogeneity of estimated benefit across studies. This may occur due to differences in host factors such as age, nutritional status, urban or rural residency, and environmental exposures. The responses of supplementation may also differ with viral, bacterial or allergic etiology. Variability in zinc salts used, the dose, the frequency, duration of supplementation and how the outcome of pneumonia is defined or monitored can also contribute largely to the heterogeneous impact. Whether and to what extent these factors might modify and tailor the beneficial effect of zinc is still unclear. Finally the most recent meta-analysis by Mayo-Wilson, et al. [13] of 80 randomized trials with 205 401 participants found no effect of zinc supplementation despite a possibly synergistic co-intervention of vitamin A on incidence or prevalence of respiratory infections and a small but non-significant effect on all-cause mortality. In conclusion, despite convincing biological rationale exists for the role of zinc in reducing incidence of infections – especially in malnourished children – the prophylactic role of zinc to prevent pneumonia in children is unresolved. It is of foremost importance to understand the predictors of zinc efficacy to identify the populations most likely to benefit from supplementation. It appears both intuitive and scientific that even if found to be prophylactically efficacious, programmatic decisions on the prophylactic use of zinc supplementation will need to address additional issues like safety, acceptability, adherence, cost and effectiveness.

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In the pre-antiretroviral therapy (ART) era, HIV infection in perinatally infected children was described to follow three distinct courses. An in utero infection coincident with immunological cell expansion in the fetus can lead to rapid spread of virus and culminates in a rapid disease course, with onset of AIDS and symptoms during the first few months of life and a median survival time of 6-9 months, if untreated. The majority of perinatally infected newborns (60-80%) in developed countries present with a much slower progression of disease, with a median survival time of 6 years representing the 2nd pattern of disease. The 3rd pattern of disease occurs in a small percentage (<5%) of perinatally infected children referred to as long-term non-progressors (LTNPs), who have minimal or no progression of disease with relatively normal CD4 counts and very low viral loads for longer than 8 years [1,2].

This variation in susceptibility to HIV-1 infection and its rate of progression is partly explained by host genetic factors. Supporting a role for genetic factors in the host, several studies have shown that susceptibility to HIV-1 in vitro largely varies among cells from genetically distinct individuals. Conversely, primary cells from homozygotic twins display much less variation in their susceptibility to infection. In order to complete a replicative cycle, HIV-1 must use the cellular machinery at multiple steps and rely on host cellular proteins. Only a fraction of these host proteins have been identified, but their role in the HIV-1 susceptibility and progression is currently a subject of intense investigation [3]. The study by Palchaudhuri, et al. [4] in the current issue is the first such study on perinatally infected Indian children linking specific genetic markers with HIV progression. Approaches used to study these host genetic factors in vitro have predominantly used LTNPs. Studies on perinatally infected children in a French cohort have demonstrated this population to be 2% of the infected population [5].

Prevalence studies have not been done in India [6].

The host genetic factors involved in HIV infection and progression can be grouped into those that modulate viral entry, those that modulate post entry viral replication, and those that modulate the innate immune response against HIV-1 infection [7]. Among factors modulating viral entry, HIV-1 co-receptor CCR5 and CXCR4 polymorphisms are being investigated. High level of wild type CCR5 expression on CD4-positive primary T cells is associated with high viral loads and accelerated disease progression. Studies have characterized the CCR5Δ32 allele, which has been unequivocally associated with protection to HIV-1 infection in homozygotic individuals. CCR5Δ32 expresses a truncated co-receptor that is not transported to the cell surface and thus is incompetent for viral entry [7]. Individuals homozygous for the Δ32 allele seem to have a normal life expectancy. Though the CCR5Δ32 allele occurs at a frequency of 4-15% in the Caucasian population, it is rarely found in Asians and Africans [8]. Recently, CCR5 promoter polymorphisms like CCR5 5902G have been described to affect HIV progression [9,10]. This allele has been described to have a high prevalence among LTNPs in the present study.

The beta-chemokines MIP-1α(CCL3), MIP-1α(CCL4), and RANTES (CCL5) are the natural ligands of CCR5, which after binding to it, induce its internalization. Thus, high levels of these chemokines are postulated to provide the host immunity against viral replication [11]. SDF-1 (also known as CXCL12) is the only known ligand of CXCR4, which also induces internalization of the receptor [12]. A polymorphism in the noncoding region of SDF-1 has been reported (SDF1-3’A). In the homozygous form, the presence of an A at position 801 has been associated with slower progression to AIDS, as compared to heterozygous or wild-type