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The Lancet's Series on breastfeeding[1,2] has shown the nutritional, immunological, and developmental inferiority of breastmilk substitutes, and the contribution of breastfeeding to the survival and health of children and their mothers in all countries. It does not, however, address the needs of the infants most vulnerable to nutritional, immune system, growth, and developmental compromise; those born preterm, growth retarded, or who are sick. These infants and their mothers need special protection and support to enable breastfeeding and feeding with breastmilk, yet paradoxically they are often denied rights normally accepted unconditionally for full term infants. The common practices in neonatal units worldwide of separation of mothers and infants, routine supplementation and fortification, and targets for weight gain, disrupt the essential close maternal–newborn contact and are counter to the evidence on the conditions needed to establish breastfeeding.[3,4] It is hard to imagine an environment that is more antagonistic to breastfeeding.

A transformational shift is needed in the way we care for these infants and their parents. This change includes the development of parents and staff as partners in care,[5] promotion of kangaroo mother care as standard, and tackling barriers to its implementation,[6] and adherence to the International Code on the Marketing of Breast-milk Substitutes to limit claims about specialised formula that lack evidence.[7] Studies have shown a substantial related economic benefit, so resource use should be no barrier. Increased use of breastfeeding and feeding with breastmilk for these babies and mothers would contribute to progress on Sustainable Development Goal 3 in relation to infant and maternal survival, health, and wellbeing. Concerted action by researchers, funding agencies, health professionals, and advocacy groups is long overdue.

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Authors' reply

We appreciate the interest raised by our Series.[1] Dylan Walters and colleagues rightly point out that the standard international indicator for exclusive breastfeeding (proportion of infants aged 0–5 months who are fed exclusively with breastmilk) is distinct from the proportion of infants who are exclusively breastfed until they reach 6 months of age. While we agree that new approaches are needed to estimate the latter from survey data, the former is the only internationally comparable indicator currently available for low-income and middle-income countries, with the advantages of not depending on recall nor relying on modelling. We disagree that the current indicator is flawed—it just represents a different metric.

John Wallingford challenges our estimate of lives saved through improved breastfeeding practices, mentioning that it is based on observational studies. We are unaware of any randomised studies on breastfeeding promotion and mortality, because these studies require large sample sizes and—because compliance with promotion is always imperfect—both intervention and comparison groups include a mixture of feeding modes. Our effect estimate was based on the few studies of mortality according to four categories of breastfeeding:[2] exclusive, predominant, partial, or none. There are many other studies comparing breastfed and non-breastfed infants, starting in the early 1900s,[3,4] all of which show increased risk of death in infants fed either formula or animal milk. Because in low-income and middle-income countries breastfeeding is more common in the poor, confounding will likely reduce the magnitude of the associations; studies with proper adjustment also document a protective effect. Whereas each individual observational study can be potentially flawed, the large effect sizes, dose–response associations with intensity of breastfeeding, and consistency of a large number of studies make the overall level of evidence strong. Wallingford's non-systematic review of the literature cites a trial from Belarus but fails to cite the other two randomised trials in Mexico and India; all three show that breastfeeding protects against

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infectious diseases.[5] The HIV study he mentions cannot be extrapolated to uninfected children. A large systematic review showed consistent effects over tens of studies regarding the protection against morbidity.[5]

Maria Quigley and Claire Carson question our estimate of 0·5% prevalence of breastfeeding at 12 months in the UK. We did an extensive review of the medical literature, and none of the published studies reported on breastfeeding at this age. We then wrote to authors of several studies in the UK, and the only estimate (unpublished) we obtained was 0·5% from the UK Millennium Cohort; the authors of this estimate are acknowledged in the appendix of our paper.[1] We double checked this low estimate with researchers involved in the UK Infant Feeding Surveys, and they found that the figure was credible. The reference to the 2010 Infant Feeding Survey appendix refers to the estimates of breastfeeding soon after birth and at 6 months; inadvertently, we omitted the information that the 12 month estimate was based on the Millennium Cohort. Based on the same cohort, Quigley and Carson now estimate that this proportion is close to 10%, but they agree that this potential inaccuracy will not affect the main conclusions of our study. We would like to add that the absence of reliable estimates on breastfeeding at 12 months is symptomatic of the low level of interest in such an important behaviour.

Marilyn Agranonik and colleagues cite unpublished results from their birth cohort on how breastfeeding could prevent obesogenic behaviours in children who are born small for age. In the literature review commissioned for this Series,[6] we did not find studies reporting on such an interaction, so we look forward to seeing their results published.

Lastly, we fully agree with Mary Renfrew on the need for a transformational shift in the way high-risk newborn babies are managed in many neonatal units. Space limitations precluded us from addressing this topic in our Series.

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Trial size, HIV pre-exposure prophylaxis, and breastfeeding

Nicolas Nagot and colleagues (Feb 6, p 566)[1] studied HIV-1 prevalence at 50 weeks in 1236 infants who were breastfed in four African countries, and diagnosed 17 HIV-1 infections. Born to HIV-1-infected mothers ineligible for antiretroviral therapy (CD4 count >350 cells per μL), the infants were randomly assigned to extended pre-exposure prophylaxis (for up to 50 weeks) with lopinavir–ritonavir or lamivudine.

Trial size considerations were referenced,[2] but not recapitulated in the study. The independent data monitoring committee advised against the planned interim analysis because, at mid-trial, fewer HIV-1 infections were diagnosed than expected: around 32 based on an anticipated 60% to 67% reduction in prevalence, such as from 5% to 2% or 3% to 1%. The number of HIV-1 infections observed at mid-term was not reported, but eight or fewer (*vs* 16 expected) might have alerted the data monitoring committee that a substantial increase in trial size would be needed to restore statistical power.

Random assignment of around 1600 infants would have given 80% power to discern a differential such as 67% reduction from 3% versus 1% HIV-1-infected infants, but around 3200 infants would have to be randomly assigned for 80% power to differentiate between 1·5% and 0·5%.

The hazard ratio for cumulative HIV-1 infection was 0·90, in favour of lopinavir–ritonavir, but the 95% CI (0·35–2·34) indicates that the true differential ranges from 67% reduction to a 50% increase in HIV-1 transmission. This uncertainty is not narrower than before the randomised trial was done, as the a-priori effect sizes have not been ruled out.

The authors conclude that infant pre-exposure prophylaxis should be extended until the end of HIV-1 exposure. This conclusion could be correct, but it does not follow directly from a randomised trial in which no infants were randomly assigned, as controls, to cessation of prophylaxis before the earlier of 50 weeks or the end of breastfeeding.

I congratulate the authors for showing that randomisation and follow-up were feasible across four sites in Burkina Faso, South Africa, Uganda, and Zambia and rejoice that pre-exposure prophylaxis has brought HIV-1 transmission rates