Commentary: Comorbidity as a factor in child health and child survival in developing countries

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Ask any clinician who has looked after children in a developing country about co-morbidity in childhood disease and you are likely to get a similar answer. Children in developing countries get ill and die in large numbers from a relatively small number of causes. Frequently they present with more than one problem and those with multiple problems are more likely to die. This co-morbidity is more than would be expected by chance alone, and is largely due to common risk factors, particularly malnutrition. This view is reinforced by studies of the aetiology of pneumonia and diarrhoeal disease in developing countries, which reveal a population of high risk, often malnourished children from whom multiple pathogens can be identified.1

These impressions are largely based on hospital experience, yet we know that most illnesses and deaths occurring in children in developing countries occur in the community rather than in health facilities. Hospitals in the developing world usually see children who have already passed through the primary health care system, and have either been recognized as seriously ill on presentation, or have failed initial treatment. Thus children with multiple problems are more likely to reach the hospital bed, whereas children presenting with uncomplicated malaria, diarrhoea, or acute respiratory infection (ARI) are usually successfully managed as outpatients. Thus hospital-based experience, or studies, cannot tell us how common, or important, co-morbidity is in the community. The innovative study by Fenn and colleagues2 in this issue of the Journal represents a rare and possibly first attempt to address this issue from a community perspective.

The paper provides a helpful definition of co-morbidity, stressing that this is co-morbidity that is more (or less) than would have been expected by chance. The authors then propose a statistical measure to assess this. In the introduction, they provide a helpful discussion of the many ways in which co-morbidity can be interpreted, but in the remainder of the paper they pay little attention to this. Importantly, remarkably little is said about malnutrition, apart from the fact that this is controlled for in the adjusted analyses. Yet malnutrition is the common factor in many of these interactions. Even WHO, notorious for promoting the ‘one death one disease’ concept through the Global Burden of Disease literature, acknowledges that in children malnutrition is associated with over half the number of deaths in each of the major categories and is by implication, an important contributory factor (http://www.who.int/child-adolescent-health/NUTRITION/child.htm). Malnutrition increases the risk of pneumonia, persistent diarrhoea, and dysentery and the likelihood of a fatal outcome.3 This can be explained on the grounds of diminished mucosal immunity, diminished protective reflexes, such as cough, and possibly diminished systemic immunity.4 In the Fenn study malnutrition is not treated as a separate condition. Had it been, we may have seen strong associations between malnutrition and pneumonia or diarrhoeal disease.

The situation with malaria is more complex. Studies of severe malaria have not shown a relationship with severe malnutrition, and some early papers claimed that malnutrition was protective against malaria, based on the observation that famine victims undergoing re-feeding are particularly susceptible to malaria.5 The WHO Comparative Risk Assessment (CRA) Project concluded that malnutrition is a major contributor to malaria morbidity and mortality, yet this conclusion is based on a small number of studies with rather contradictory results.6 For example the conclusion that malnutrition increases malaria morbidity is largely based on a single study from Vanuatu in

which malnourished children were found to have an increased probability of having had *Plasmodium vivax* infection in the previous 6 months, but no increased probability of *Plasmodium falciparum*, which was more common in the community.\(^7\) The true nature of the relationship between malnutrition and malaria remains unclear and is an important area for further research.

In malarious areas a significant proportion of children have parasitaemia at any time. Thus one should find a high degree of apparent co-morbidity with other conditions, even if it is not more than one would expect by chance. The study of Fenn *et al.* is weak in this area, as there are too few data points, yet there is an intriguing trend towards negative co-morbidity. This could be explained by suppressive effect of fever and acute phase reactants on asymptomatic parasitaemia.\(^8,9\) More has been written about the co-morbidity of malaria and ARI than other co-morbidities, yet the field remains unclear.\(^10,11\) Bacterial pneumonia may suppress parasitaemia for the reasons outlined above; other causes of pneumonia may be immunosuppressive, potentially having the opposite effect. Then there is the issue of the pulmonary pathology associated with malaria, which is believed to produce X-ray changes, and clinical signs indistinguishable from pneumonia. This leads to the most difficult problem of all. Pneumonia, in this and other field based studies, is defined as cough with fast breathing. Yet cough is ubiquitous, and fast breathing is a feature of both severe malaria and severe diarrhoea with dehydration.\(^12\) In both cases it is indicative of severe, more complicated diseases with higher risk of a fatal outcome. Severe dehydration leads to metabolic acidosis, with associated hyperventilation. Severe malaria results in tachypnoea due to direct pulmonary pathology, metabolic acidosis, or both. Thus, we should expect to see apparent co-morbidity between these conditions, with co-morbidity associated with a fatal outcome, even if the apparent co-morbidity is only a manifestation of diagnostic confusion.

In the case of diarrhoea and pneumonia this is seen in the Fenn study. The expected relationship between malaria and pneumonia is not seen; rather a negative association is found.

The Fenn study has produced a mixture of expected and unexpected findings. It is unlikely that the latter will change the way clinicians think about different disease interactions. It is more likely that this will prompt discussion of the significant shortcomings of this study. The use of IMCI definitions may not be ideal. These are designed to provide inclusive, sensitive disease categories to ensure that, for example, most children with pneumonia receive antibiotics and most children with dehydration receive fluids. They are not suitable for epidemiological studies due to their lack of specificity. It is also clear that in the Fenn study they are being applied very liberally. For example, it is unlikely that the true prevalence of diarrhoea with dehydration was 13.3–17.7%. That would suggest that all children under 2 years of age had diarrhoea with severe dehydration for 61 days each year on average, one day out of six. Similarly, the rates of pneumonia seem high. The more ‘soft’ definitions are used, the more difficult it is to interpret a study such as this. An ideal study of co-morbidity would be undertaken prospectively, with specific definitions, where possible supported by laboratory tests. This would be a substantial and costly undertaking. Even with such a study, it may be impossible to separate the specific infection of malaria from the syndrome of pneumonia, and we may eventually conclude that malaria is but one of the many specific causes of the syndrome of pneumonia.

Some may question the value of a detailed, prospective study of co-morbidity. We know that malnutrition worsens the risk of pneumonia and diarrhoea. It might be useful to quantify this risk at community level, but is it likely to alter strategies for prevention or case management? Predicting the overall impact of the removal of one disease from the community, including co-morbidities, will help in the prediction of the impact of intervention strategies, but as the experience with insecticide impregnated bed nets has shown, it is only in the context of a trial that the impact of a specific intervention can be measured with any accuracy.\(^13\) The true reasons for proceeding with this sort of research are more profound. Our understanding of the causes of illness and death in children in developing countries is truly rudimentary. Although global mortality in children <5 years of age exceeds 10 million deaths per year, our understanding of the causes of those deaths is limited to extrapolation from hospital-based studies, interpretation of structured interviews with the families of the dead children, or in some cases interpretation of specific, field based interventions.\(^14\) A much greater effort in this area should see more detailed investigation of deaths, covering both co-morbidity of pathological conditions, and the co-existence of specific social, economic, and geographic factors with cause of death. Perhaps specific interventions aimed at the prevention of malnutrition will have a major impact on mortality from pneumonia and diarrhoeal disease. Perhaps they will also have an impact on malaria. In its obsession with the application of technological solutions to complex social and economic problems, the international community has developed targeted approaches to control acute respiratory infections and diarrhoea, and is now promoting vaccines against the specific aetiological agents responsible for ARI and diarrhoea. The fact that most deaths due to these causes are really the result of malnutrition and poverty seems to be conveniently forgotten.

The study by Fenn and colleagues should stimulate a range of studies, both retrospective and prospective. It should also stimulate more detailed studies of the epidemiology of child death in the community, by cause, and particular studies of important interactions, such as between malaria and pneumonia, as well as interactions between these conditions and other factors. Most importantly it should stimulate intervention studies that measure the impact of broad, community based nutritional interventions on child mortality by cause. That would lead to a better understanding of the conditions in question, their management and their prevention, and would show countries a way out of the relentless cycle of poverty, malnutrition and child mortality. For over 20 years the global health community has been wringing its hands over the issue of child death in the developing world, yet the research effort has been largely limited to small descriptive studies and trials of specific interventions. Incredibly this effort has declined substantially since 1990 (H Campbell, personal communication). The fact that the study by Fenn and colleagues is the first of its kind reflects this global scientific neglect, which persists to the present day.

References


