

Updating the DALYs for diarrhoeal disease

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Estimates of global disease burden remain high on the international research and policy agenda as a forum for ranking health priorities. Within this, the quality of life or years lived with varying degrees of disability has been recognized as an important outcome that should be considered alongside estimates of mortality. Recent studies into the long-term consequences of diarrhoeal diseases on physical and mental development suggest that the disability adjusted life year calculations for these conditions could require updating.

Major advances in understanding the global burden of disease have been made by incorporating the quality of life affected by disabilities (i.e. years lost to disability with non-fatal conditions, injuries and diseases; or YLD) into the calculations alongside age-specific mortality (years of potential life lost to fatal conditions; YPLL). Disability adjusted life years (DALYs) represent the composite measure of YPLLs and YLDs (in which perfect health is weighted as zero disability, and disability weights progress up to one, the equivalent of death) [1].

Such analysis has brought appropriate attention to conditions such as neuropsychiatric diseases or depression that kill few, but disable many. Similarly, when consideration is given to the long-term effects of intestinal helminths on growth, fitness and even cognitive function [2,3], the DALYs for these infections can be essentially doubled [4]. Indeed, the disability component of the DALY calculations for malnutrition and the 'tropical cluster' (trypanosomiasis, Chagas disease, schistosomiasis and leishmaniasis), similar to neuropsychiatric conditions, chronic obstructive lung disease and rheumatoid arthritis, outweigh their mortality components [2,5]. Despite this, the calculated DALYs for all diarrhoeal diseases by Murray and Lopez comprised 95% mortality and only 5% disability [from the transient 10% incapacitation during overt diarrhoeal illness (i.e. liquid stools)] [1]. No long-term disability from repeated dehydrating and malnourishing diarrhoeal illnesses in the crucial, formative developmental first two years of life is

considered, largely because there had been no data to suggest such long-term effects [5].

Potential long-term morbidity

Obtaining data implicating specific diseases or conditions with long-term impaired outcomes is problematic. Despite the lack of a specific single drug (such as albendazole for intestinal helminths) to control diarrhoeal diseases, a long-term cohort study in Northeast Brazil now suggests that the four to eight dehydrating, malnourishing diarrhoeal illnesses that often occur each year in the first two years of life could have profound, lasting consequences for impaired fitness, growth, cognitive development and school performance several years later (Box 1).

Initial studies showed reduced physical fitness four to six years later associated with early childhood diarrhoea and, specifically, with cryptosporidial infections in the first two years of life, independent of respiratory illnesses, anthropometry, anemia and intestinal helminths [6]. The fitness deficits alone are comparable with that associated with a 17% decrement in work productivity [7]. Growth deficits were also evident, with early childhood diarrhoeal illnesses resulting in a growth shortfall of 3.6 cm at seven years of age, even after controlling for early childhood intestinal helminthic infections [8]. This is supported by work from Peru, where cryptosporidial infections (even sometimes without overt diarrhoea) in young or stunted children predispose to an average 1 cm growth shortfall one year after infection [9,10]. The work in Brazil has also shown early childhood diarrhoea to be associated with long-term cognitive deficits [5,11] and, more recently, educational performance*. All these effects should be seen as a best-case scenario because they were conducted in a population under close, long-term surveillance in which substantial improvements in disease rates and in nutritional status over several years

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have been documented [12]; these are improvements that have not been observed in other nearby shanty town communities.

These potential consequences of early childhood malnourishing and dehydrating diarrhoeal illnesses should not be a great surprise when considering the importance of the early years; major growth and synapse formation occurs during the first two years of life [13]. If impaired at this formative stage, it might be difficult to compensate or build these synapses later in life.

The importance of an accurate YLD assessment from early childhood illnesses such as diarrhoeal diseases is further accentuated by the striking relative shift from mortality to morbidity observed over recent decades. Despite marked reductions in diarrhoea mortality since 1955 (from 4.2 million to <2.5 million) [14,15], the morbidity rates of two to four illnesses per child per year have not decreased. Instead, with increasing populations in developing regions, the total global morbidity burden from diarrhoea has actually increased[†].

Refining DALYs

The current DALY estimate for diarrhoeal disease is ~100 million, with >95% owing to mortality (Box 2) [16]. If only 5% of children who experience an average of four to eight repeated episodes of diarrhoea in their first two years of life are assumed to incur a lifelong disability in the lowest disability class, then this could double the total DALYs for diarrhoea. For every 5% increase in the proportion of children at risk, the total DALYs would increase by 100 million. Our data, although limited, suggest that up to half of the children in an impoverished, urban shanty town in Northeast Brazil could experience a 4–5% long-term decrement in physical and cognitive function, the former roughly equivalent to a 17% decrement in work productivity. Thus, with 80% of the world's population now living in Asia, Africa and Latin America, it might be readily expected that 10–25% of the world's children might experience long-term disability at the lowest level. Even if this

[†]M. Kosek and R.L. Guerrant, presented at WHO, September 2000.

Box 1. Evidence for lasting disability effects from early childhood diarrhoea

Fitness impairment

Early childhood diarrhoea, ECD (at 0–2 years old), associates with impaired fitness scores (assessed by the Harvard Step Test, HST) 4–7 years later (by 4% and 8.2% for median and high diarrhoea burdens, respectively [a]); for comparison, fitness scores improved by 6.9% four months after albendazole treatment of schoolboys in Kenya [b], and a 4.3% increase in HST scores correlated with a 16.6% increase in work productivity in sugar cane cutters in Zimbabwe [c].

Growth shortfalls

- Cryptosporidial infections and persistent diarrhoea predispose to increased diarrhoea morbidity and nutritional shortfalls for up to 18 months [d–f].
- Cryptosporidial infections at <6 months of age and in stunted children predispose to 0.95–1.05 cm growth deficits one year later [g].
- Early childhood diarrhoea (at 0–2 years old) associates with lasting growth shortfalls, persisting at 3.6 cm at seven years old, and additive to 8.2 cm with intestinal helminths at 0–2 years old [h].

Cognitive impairment

- Early childhood diarrhoea correlated with impaired cognitive function at 6–9 years old by McCarthy Draw-A-Design ($P = 0.017$ when controlling for early childhood helminthic infections), and Wechsler Intelligence Scale for Children (WISC) coding and reverse digit span testing ($P = 0.045$) [a].
- Early childhood diarrhoea (at 0–2 years old) associates with impaired Test of Nonverbal Intelligence (TONI-III) scores at 6–10 years old, when controlling for maternal education, breast-feeding duration and early helminthic infections; and WISC coding and digit span scores were lower in children who had one or more persistent diarrhoeal illnesses in their first two years of life [i].

School performance (increased age at starting school and age-for-grade)

Early childhood diarrhoea correlates with delayed age at starting school and older age-for-grade; this is independent of maternal education, socioeconomic status, other illnesses and significant effects (of ECD) on

height-for-age Z scores (i.e. stunting) at 0, 2 or 7 years of age ($P < 0.02$, $n = 77$) (B. Lorntz *et al.*, unpublished). In addition, late starters are twofold more likely to have experienced cryptosporidial infections in their first two years of life*.

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Box 2. Revised DALY calculations for diarrhoeal diseases

Disability adjusted life year (DALY) calculations for diarrhoeal diseases are assessed following the standard formulas with age-weighting and discounting at 3%, and all disability falling into the lowest class (weight of 0.096). The mortality in all ages of 2 946 000 cases contributing to 95 371 446 DALYs (89% in 0–4-year-olds), and the morbidity in >4-year-olds, with 1.8 billion attacks of one week duration (0.02 years) contributing 42 778 414 DALYs, remains fixed (Table I). In Table I, scenario 1 applies the original assumptions by Murray and Lopez of 2.27 million attacks of one week duration, in which the 1.3 million DALYs from morbidity in 0–4-year olds represents 1% of the total of 100.9 million global diarrhoea DALYs. Scenario 2 assumes that 17% of 0–4-year-olds (or 33% of half of the world's children at greatest risk) are at risk of at least one diarrhoeal attack (or a diarrhoea burden) that could have lifelong disability (with a life expectancy of 81.25 years as used by Murray and Lopez). Scenario 3 assumes that 25% of 0–4-year-olds (or half of the most impoverished 50% of the world's children) are at lifelong risk. Scenario 4 assumes that 10% of 0–4-year-olds experience a lifelong disability; scenario 5 assumes that this lasts only 25 years. Scenario 6 assumes that only 5% of 0–4-year-olds are affected.

For every 5% of children affected lifelong, DALYs increase by ~100 million; 25% of children affected would increase current DALY estimates by over sixfold; only 5% affected lifelong (or 10% affected for only 25 years) would more than double the total global diarrhoea DALYs.

Table I. Morbidity of 0–4-year-olds for six scenarios^a

Scenario	Attack rate per year	Proportion disabled	Duration of disability (years)	DALYs for morbidity in 0–4-year-olds ($\times 10^6$) ^b	Total DALYs ($\times 10^6$)
1	3.6	1	0.02	1.3	(1) 100.9
2	1	0.17	81.25	351.7	(78) 451.3
3	1	0.25	81.25	517.2	(84) 616.8
4	1	0.10	81.25	206.9	(68) 306.5
5	1	0.10	25	118.1	(54) 217.7
6	1	0.05	81.25	107.6	(52) 207.2

^aAbbreviation: DALY, disability adjusted life year.

^bPercentage of total DALYs included in parentheses.

duration was only for 25 formative years, affecting only 10% of the 0–4-year-old children, it would still more than double the global diarrhoea DALY calculation.

This increase in the burden of diarrhoeal disease is conservative because it excludes even subclinical enteric infections that might alter crucial absorptive function and nutritional status [10,17,18]. Such alterations might impede the absorption of (and potentially thus enhance resistance to) key anti-HIV or anti-tuberculosis drugs [18–20].

Conclusions

There is a growing body of evidence to suggest that the morbidity impact of diarrhoeal diseases and enteric infections, especially in early childhood, could actually outweigh the burden of its mortality. Crucial to furthering our understanding in this area is: (1) the acquisition of substantial information concerning the potential long-term correlates with illness rates and even subclinical infections, controlling for the numerous possible confounding variables; and (2) careful studies of potential interventions that could alter these adverse outcomes. Only improved data and careful,

accurate analyses will allow a more-precise assessment of the full costs of these common diseases, and thus the potential benefits of effective interventions that prevent or reduce these costs.

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Invasion of skin by *Schistosoma cercariae*



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Schistosomiasis caused by *Schistosoma* spp. remains a major global health problem affecting >200 million people. The success of these parasites is a result of their adaptation to several different environments, including snail tissue, fresh water and mammalian blood; and their ability to switch between these environments rapidly. The initial step in infection of the human host involves penetration of the human skin by the aquatic form of *Schistosoma*, the cercaria. This aspect of host invasion is remarkable because no wounds or insect vectors are required and cercariae can penetrate through intact skin rapidly. The mechanisms of host finding and invasion represent fascinating and complex biological phenomenon, which are discussed here.

Schistosomiasis is an ancient disease, widespread among various vertebrates. *Schistosoma* and related trematodes can infect various hosts ranging from fish to fowl to humans. Human schistosomiasis results primarily from the host human immune response to parasite eggs deposited in the host tissue by adult worms (Fig. 1). However, initiation of infection requires a multicellular cercaria to find a host in fresh water and to penetrate through intact skin.

Taking biological advantage

Host finding and invasion by schistosome cercariae are noteworthy examples of biological adaptation, which have been studied in several *Schistosoma* spp. As expected, the specific host-signals recognized by schistosomes vary with

specific host–parasite interactions. In the case of schistosomes that infect humans, cercariae are positively phototropic and will therefore congregate towards the surface of shallow waters where human contact would be maximized [1]. Cercariae follow a thermal gradient as the means of finding their host (see animation at <http://archive.bmn.com/supp/part/part0502.html>). Upon contact with human skin, cercariae respond to chemical signals, particularly medium-chain free fatty acids, as a signal for skin invasion (for more details of these initial steps, see Refs [1–5]).

Following stimulation by medium-chain free fatty acids, such as linoleic acid, cercariae will begin secreting gland contents from the acetabular gland complex. This complex comprises a set of cells found in the