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Invited Review

Estimating the global distribution and disease burden of intestinal nematode infections: Adding up the numbers – A review

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ABSTRACT

Intestinal nematode infections are among the most common infections of humans in developing countries, but precise estimates of the populations at risk of infection, morbidity and mortality are difficult to derive. Careful evaluation of the global distribution and disease burden of nematodes is essential to determine the cost-effectiveness of control and ensure that control programmes are focused appropriately. In turn, understanding the disease burden depends on a summary measure of health as well as reliable data on risks of infection, morbidity and mortality. This review provides an overview of data sources and methods adopted in the Global Burden of Disease study to estimate the burden of intestinal nematodes, including the empirical and modelling challenges in its estimation. Particular attention is paid to efforts to improve our ability to define at-risk populations, based on a Global Atlas of Helminth Infection, and to better estimate attributable morbidity.

1. Introduction

It is in the very nature of parasitologists to count things. Little time passes without a publication presenting a revised set of estimates of numbers infected with parasite A or suffering from clinical condition B. For those of us working in helminthology, this heritage of enumeration originates with Norman Stoll when, during his presidential address to the American Society of Parasitologists in Boston in December 1946, he posed the question: "just how much human helminthiasis is there in the world"? His response was based on thoroughly researched work, inspired by his early overseas work in China, Panama and Puerto Rica, and World War II service on Guam. The resultant 1947 paper, entitled This Wormy World (Stoll, 1947), presented the first systematic attempt to measure the worldwide impact of human parasitism by helminths, and probably remains one of the most widely quoted publications in helminthology.

Of the 341 helminth species found to infect humans (Coombs and Crompton, 1991), Stoll only considered 25 as having sufficient global significance to merit large-scale control programmes (Stoll, 1947). Among these, intestinal nematodes (or soil-transmitted helminths: *Ascaris lumbricoides*, *Trichuris trichiura* and the hookworms, *Necator americanus* and *Ancylostoma duodenale*) were estimated by Stoll to be the most prevalent helminth species worldwide. More recent estimates suggest that intestinal nematodes continue to infect more than one billion people (de Silva et al., 2003; Bethony et al., 2006). Stoll's estimates, in common with all estimates since (Le Riche, 1967; Peters, 1978; Walsh, 1984; Crompton and Tulley, 1987; Crompton, 1988, 1999; Bundy and Cooper, 1989; Bundy, 1994, 1997; Chan et al., 1994; Brooker et al., 2000), are based on extrapolation from available empirical data. Stoll recognised, however, that among the biggest hurdles to answering his question was the lack of quality data on infection prevalence (Stoll, 1947). Moreover, prevalence indicates little more than presence or absence, and only a fraction of infections will be associated with morbidity. This is because morbidity due to intestinal nematodes is related to the intensity of infection (worm burden) and the most intense infection occurs in a minority of infected individuals (Anderson and May, 1991; Bundy and Medley, 1992).

Again, Stoll posited the pertinent question: "how approach the assignment of a consideration of the problem of helminthic infection as the cause of disability and disease in the tropics?" (Stoll, 1957). Direct estimates of morbidity due to nematode infection would be preferred, but national health statistics are unreliable because signs and symptoms of infection are generally non-specific, chronic and insidious, and hence often go unreported (Bundy et al., 2004). Instead, estimates have been based on approximations from available data on the prevalence of infection (Chan et al.,

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1994; Chan, 1997; Bundy et al., 2004). This type of analysis is obviously crude, but formed the basis for estimating the disease burden due to intestinal nematodes in the Global Burden of Disease (GBD) study (Murray and Lopez, 1996; Mathers et al., 2007). Since the initial GBD study, there has been considerable debate concerning burden estimates for helminth infection (Chan, 1997; Hotez et al., 2008; King and Bertino, 2008), especially schistosomiasis (King et al., 2005; Jia et al., 2007; Finkelstein et al., 2008; Hotez and Fenwick, 2009). Notably absent, however, is an understanding of how the estimates for intestinal nematode infections were derived.

Here, I provide a brief review of the methods previously used to estimate the burden of disease due to the intestinal nematodes *A. lumbricoides*, *T. trichiura* and hookworm. I also discuss the empirical, methodological and conceptual limitations of the approach and identify areas requiring further investigation. In particular, I highlight work which has sought to develop a Global Atlas of Helminth Infection in order to provide a better estimate of the global distribution of infection.

2. Measuring the burden of disease

The measurement and comparison of the burden of different diseases necessitates (i) a common metric and (ii) consistent descriptions of key epidemiological parameters, based on the best available information. In the first half of the 20th century, the burden of parasitic diseases was considered from a strictly clinical perspective, focusing on the number of deaths. From the 1960s onwards, researchers began to additionally consider the economic effects of diseases, including studies that investigated the effect of parasitic diseases on worker productivity (Farooq, 1964; Fenwick and Figenschou, 1972; Weisbrod, 1974; Guyatt, 2000). However, estimation procedures based on mortality or productivity fail to sufficiently capture the non-fatal health outcomes of diseases and impact on non-working populations. This omission is especially relevant for intestinal nematodes which are rarely fatal and common among children.

An early attempt to quantify the relative importance of different diseases was the Ghana Health Assessment Project (Ghana Health Assessment Project Team, 1981) which measured the impact of a given disease on a community in terms of the number of healthy days of life lost through illness, disability and death. The measure was derived from a synthesis of information on incidence, case fatality rates and the extent and duration of disability arising. The intention of the researchers was to use this measure to identify priorities for allocation of resources and to estimate the number of health days of life saved by different interventions in relation to the costs of intervention. This approach was later expanded upon in the GBD studies.

The initial GBD study was commissioned by the World Bank in 1992 and sought to provide a comprehensive assessment of disease burden in 1990 (Jamison et al., 1993; Murray et al., 1994; Murray and Lopez, 1996). The study developed a conceptual and methodological framework for the assessment of morbidity and mortality across 107 diseases and injuries and introduced a new metric to quantify disease burden, the Disability-Adjusted Life Year (DALY). This metric combines both years of life lost from premature death (YLLs) and years of life lived with disability (YLDs), translating disabilities into years of healthy life lost by giving each disease state a disability weight ranging from 0 (healthy) to 1 (death). Estimates of disease burden were provided for each sex and among five age groups for different regions of the world, based on empirical estimates of disease incidence, duration of disease, case fatality and mortality. The estimates were calculated on the assumption that each disease condition can only be attributed to a single cause and that can be reliably measured.

The overall goal of the GBD study has been to provide internally consistent, summary measures of disease burden for purposes of cost-effectiveness analysis and priority setting. New estimates for 2001, incorporating methodological developments as well as an analysis of the contribution to disease burden of major risk factors, were published as part of the second revision of the Disease Control Priorities Project (Lopez et al., 2006; Mathers et al., 2006Lopez et al., 2006). In 2007, a new GBD study was launched with the aim of producing comprehensive and comparable estimates of the burden of 175 diseases and injuries and 43 risk factors in 21 regions of the world for both 1990 and 2005, based on new data and improved techniques (Murray et al., 2007; Anon., 2008). Since its inception, the GBD study has attracted unending debate. Much of this has focused on the methods used to assess the severity and age weightings for disease conditions (Anand and Hanson, 1997; Williams, 1999; Gold et al., 2002), less discussion has focused on the uncertainty of the descriptive epidemiology for some populations, especially in sub-Saharan Africa (Cooper et al., 1998). This latter challenge is particularly relevant for intestinal nematodes – see below.

Estimates from the GBD study incorporate information on four main features of each condition: (i) what is known about disease occurrence – incidence and/or prevalence; (ii) the disability weight assigned to each condition; (iii) the risk and duration of morbidity; and (iv) the risk of mortality. The data sources and approaches to estimating these features for intestinal nematodes are now considered in turn.

3. Estimating prevalence of infection: Towards a Global Atlas

Reliable estimates of the national and sub-national variation in infection risk are essential for burden estimation, especially as there are marked geographical differences in risk (Brooker et al., 2006). Infection is most prevalent among rural communities in warm and humid equatorial regions and where sanitation facilities are inadequate. Infection also occurs in urban areas. Even within areas of low prevalence, small localised areas of high prevalence can exist. Only cold or very hot, arid climates are free of infection. The absence of infection in temperate areas is probably due to historical improvements in hygiene and sanitation. Over the last two decades, in middle-income countries such as China and Brazil, there have been precipitous declines in prevalence (de Silva et al., 2003), primarily due to urbanisation and economic development (Hotez, 2008). Such poverty reduction, together with a shift to a more urbanised economy, was thought to play an important role in the elimination of hookworm in the American South during the early 20th century (Bleakley, 2007).

Until recently, very few countries had conducted national surveys of intestinal nematodes. Perhaps the largest surveys are those conducted in China in 1990 and 2003, where over 300,000 individuals were sampled across the country (Xu et al., 1995; Coordinating Office of the National Survey on the Important Human Parasitic Diseases, 2005). Findings indicate that prevalence of intestinal nematodes fell from 53.6% in 1990 to 19.6% in 2003. National surveys have also recently been conducted in a number of African countries, including Angola, Burkina Faso, Mali, Malawi, Mozambique, Niger, Sierra Leone and Uganda. In countries without comprehensive data, estimates of national prevalence are extrapolated from the available prevalence surveys that have been undertaken. In certain countries, however, very few surveys exist and these have typically been conducted in areas of known high prevalence, potentially over-estimating national prevalence (Brooker et al., 2000).

In an effort to collate available prevalence data into a single resource, a Global Atlas of Helminth Infection was launched with the