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Finding information about the burden of disease☆

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This article is based on a chapter of a new book, *Clinical Epidemiology: How to Do Clinical Practice Research*, which is about designing and conducting practical research in clinical settings.

1. Clinical research scenario

I had a recent opportunity to be a member of an interagency working group composed of investigators from the University of Ottawa (led by George Wells and Karin Källander), the Karolinska Institute, the United Nations Children's Fund, and the World Health Organization (WHO) to develop a protocol to evaluate home and community management by volunteering community mothers to reduce the mortality from malaria and pneumonia in children under 5 years of age in endemic low-income countries. Malaria and pneumonia each cause more than 20% of all childhood deaths in sub-Saharan Africa [1,2]. Delayed therapy is thought to be a major remediable factor for reducing this mortality [3]. Fever is the commonest clinical presentation for malaria, and cough with an increased respiratory rate is the commonest clinical presentation for pneumonia. As many as a third of sick children in health centers suffer from overlapping symptoms of malaria and pneumonia, and given the lack of laboratory equipment, these two conditions are frequently indistinguishable by mothers and other caregivers [4]. For malaria, the WHO Roll Back Malaria strategy recommends prompt administration of an effective antimalarial, preferably on the first day of fever [5]. In Ethiopia, a randomized controlled trial of teaching mothers to provide home treatment for malaria demonstrated a 40% decrease in overall child mortality [6].

This does not solve the challenge of the residual mortality from pneumonia and can even cause increased delays in health seeking and treatment for pneumonia symptoms. In view of the impossibility of community mothers reliably distinguishing between malaria and pneumonia, it is logical for the mother to give both the antimalarial and an antibiotic to children with overlapping symptoms. However, there is reluctance to give mothers a supply of antibiotics because of the concern that excessive prescribing will lead to increased antibiotic resistance. This concern could be countered if it can be shown that home and community therapy does more good than harm compared with continuing to rely on distant, and often absent, health care workers.

A two-arm controlled trial in six countries is being proposed to assess the impact that a program that educates families/community mother volunteers and provides a sustainable drug supply of antimalarials and antibiotics will have on child survival. In the ''malaria-only'' arm, mothers will receive family/community access to antimalarials through a trained community mother volunteer but will have to get antibiotics from health facilities. In the ''combined'' arm, the mothers will have access to both antimalarials and antibiotics from the community volunteer.

Justifying such a trial, especially when resources for carrying it out are likely to be scarce, requires documenting the ''burden of disease.''

2. Finding and using burden of disease evidence

One of the most important ingredients of justifying a research study is the accurate portrayal of mortality risks, distressing symptoms, disability (mental and physical), and the economic burden of diseases that the study will seek to prevent or treat. These ingredients fall under the rubric ''burden of disease,'' which can be defined as the effects of disease on the physical, emotional, and social well-being of the individual. Although some semblance of this information can be retrieved from many sources, including the studies in systematic reviews, it is often obtained from selected populations or passed along from author to author, with the original source being lost or poorly justified. In this article, we will delve into the intricacies and mysteries of finding solid information about the burden of disease.

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Surprisingly little work has been done on defining how to best search for this information, how much detail to include in a grant submission, and how to avoid bias. This last issue may seem surprising to those of us who glibly or gullibly cite dry and often inflated population statistics from the introductory section of a standard text in our applications for research funding. However, there is an understandable temptation to be selective in using data to justify the importance of the problem you wish to study. Most individuals have more than one disease in their later years—just look at all the conditions listed on a death certificate—but the champions for each disease try to attribute all of the morbidity and mortality to the disorder in which they are interested. One problem with this is that when a study includes those individuals with only the one condition of interest, the risk for adverse outcomes often falls dramatically, so that the ensuing investigation ends up being hoisted on its own justification and underpowered for comparing interventions or exploring other hypotheses. Furthermore, even if all comers are accepted into an investigation, if the intervention is directed at only one condition, the effect will be diluted or drowned because of the competing conditions that can contribute to a given patient's demise. So what data should one include in justifying a study and planning its execution?

Although the WHO adopted an enlightened, inclusive definition of health in 1948 as "a state of physical, mental, and psychological well-being, and not merely the absence of disease," for many years the focus in assessing burden of illness was on premature mortality. Mere enlightenment is usually not enough to quickly change the way we do things, so it took quite awhile after the announcement of the WHO's holistic definition for the burden of illness statistics to reflect this. Until the 1990s, conventional measures of health status included life expectancy, infant mortality rate, and disease-specific morbidity events (e.g., number of myocardial ischemic events). These individual measures were universally used to provide the basic framework of indicators of health status even though they could not be used for comparisons of one disease condition with another or be summed across disease conditions for comparing one group of people with another. Lack of a common measure for health status made direct comparisons over time or of one group with another impossible despite the dramatic changes occurring due to the "epidemiologic transition" in countries from high to low premature mortality rates; this was characterized by changes in disease profile and age composition, that is, (a) reduced incidence or prevalence of infectious diseases, (b) increased prevalence of noncommunicable and degenerative diseases, and (c) increase in the proportion of elderly and geriatric individuals in a population.

At the end of the 20th century, 52 years after its founding, the WHO established the Global Burden of Disease initiative and adopted a set of summary measures of population health status and reported these in its annual World Health Report [1], including a set of health status measurements for different countries using the "disability-adjusted life-year" (DALY) as the unifying metric that combines the impact of diseases on mortality as well as morbidity. This is the number of fully healthy life-years lost to a particular disease or condition or risk factor. It incorporates the age at which the death occurs and the duration and severity of any disability created. Note in the figures that disabling conditions such as mental health and musculoskeletal diseases are missing from the mortality tables (Fig. 1) but dominate the disability measures (Fig. 2 and Table 1). These data are also available by condition for most clinical conditions, such as those in Table 1, summarized by country.

A major strength of the DALY is that it provides a standardized metric so that the sum of mortality and morbidity can be compared across conditions. This metric also handles "competing risks": it allows each individual to die only once! Previously, if a person died with two diseases such as diabetes and cardiac decompensation, the diabetes and cardiovascular advocacy groups each claimed the death.

The Global Burden of Disease initiative has been extremely controversial, mainly because the data were unavailable for most lower- and middle-income countries and, therefore, had to be estimated [8].

Inequity or unfairness in the distribution of the burden of disease must also be considered. In most cases, disease is more prevalent among the poor and disadvantaged. Conversely, if the relative benefits of intervention are stable across populations, the poor and disadvantaged will have greater absolute benefit from a prevention or cure than the more privileged [9]—providing, of course, that they receive the intervention.

Let's take the Home and Community Management of Malaria and Pneumonia project described at the beginning of the chapter and look at how we went about assessing the burden of disease from these conditions and how we might have done better.

> Search strategy: We searched MEDLINE using the keywords "malaria and burden and review," retrieving 55 hits of which 11 were relevant, and we searched with the terms "pneumonia and Africa and burden and review," yielding five hits of which two were relevant with useful references although not comprehensive.

This could clearly have been done better, by searching for original articles as well as reviews and by using a powerful search strategy, such as the one for systematic reviews in PubMed (http://web.ncbi.nlm.nih.gov/entrez/query/static/clinical.shtml). Amends will be made later in this article.

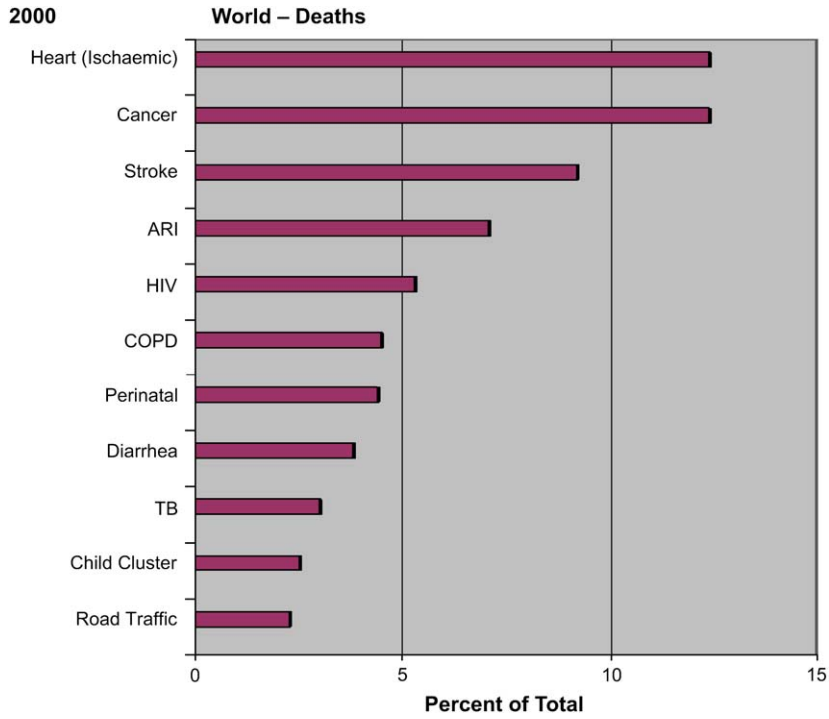

Fig. 1. World Health Organization estimates of worldwide deaths by cause for the year 2000 as a percentage of total mortality. ARI, acute respiratory illness; HIV, human immunodeficiency virus; TB, tuberculosis; COPD, chronic obstructive pulmonary disease; Child Cluster, childhood illnesses.

Another generic approach to finding information on the burden of disease is to "Google" it (http://www.google.com). In this case, a search on Google for "malaria burden of disease" produces a first page link to the malaria part of the Web site of the World Health Report described above: http://www.who.int/rbm/Presentations/MIP-RBM-final/tsld002.htm. This Web site cites 300–500 million clinical cases per year, with 80% of these cases in Africa, and a million deaths per year, with 90% of deaths in Africa, and substantial disability, 40 million DALYs lost annually.

In the appendices of the main WHO report (http://www.who.int/whr/2002/en/), we can also find that lower respiratory infections were responsible for 6.8% of all deaths in the world at all ages. In Africa, there were 1 million deaths and 31 billion DALYs. The methodology in the main report reassures us that the total number of deaths could not exceed the sum of the deaths attributed to individual conditions and that these numbers do not reflect double counting—individuals can only die once.

It is also important to include the economic burden of illness. This term includes the following different aspects:

1. What is the value of disability from the condition of interest and of the loss of life to the affected individual and to society?
2. What are the economic costs in foregone benefits arising because of the mortality and disability from this condition?

Here is an example of how to look for this information:

> To check on the economic burden, we searched MEDLINE (via the Ovid interface) using the keywords "malaria and economic burden" (46 hits; 11 useful) and "pneumonia and economic burden" (45 hits; 10 useful). Again, Google came up with some complementary hits, including, for malaria and economic burden, one of the seminal articles by Gallup and Sachs [10].

Our searches produced some useful citations, but for a research proposal it is important to be comprehensive. Clinical investigators are not usually adept literature searchers, so it is wise to seek the assistance of a medical librarian who can help you ensure that you are searching the appropriate databases and information sources as well as using the best strategies [11]. One of the authors (J.M.), an experienced librarian, accounts how she went about the search with a view to showing you "expert-level" searching, allowing you to follow along, illustrating that searching is an iterative process, and providing a few tips that you may be able to use yourself or negotiate with a librarian.

This approach begins with reviewing the search question, separating it into concepts or elements that can be searched separately, making sure to identify the patient,

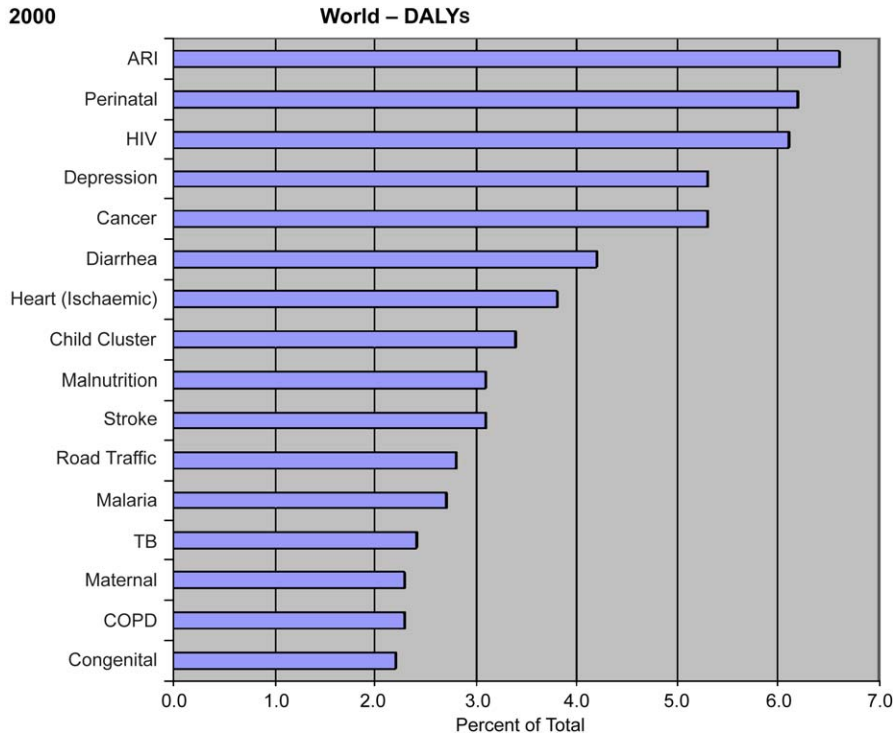

Fig. 2. World Health Organization estimates of disability-adjusted life-years (DALYs) by cause for the year 2000 as percentage of total disability. ARI, acute respiratory illness; HIV, human immunodeficiency virus; Child Cluster, childhood illnesses; TB, tuberculosis; COPD, chronic obstructive pulmonary disease.

intervention/comparison, and outcome. When searching in any database, she uses the controlled vocabulary of indexing terms for that database. In MEDLINE, the indexing terms are called Medical Subject Heading (MeSH), and this is the most efficient way to begin searching the database.

Filters can be used depending on the type of clinical or research question being addressed. Some examples include limiting articles to publication types (i.e., meta-analysis, clinical practice guidelines) or animal types or language [12,13]. In this case, a filter is added for burden of illness. The concept of burden of illness is indexed in both the MEDLINE and EMBASE databases with the subject heading ''cost of illness.'' Although the definition in MEDLINE has ''cost'' in it, the emphasis is meant to be on social costs (to society or the individuals concerned) rather than monetary costs. The MeSH term ''burden of illness'' was introduced in 1993. From 1966 to 1992 it was indexed under ''costs and cost analysis.''

Table 1
The leading causes of years lived with disability, worldwide, 1990

Condition	Total (millions)	Percentage of total
All causes	472.7	100
Unipolar major depression	50.8	10.7
Iron deficiency anemia	22.0	2.7
Falls	22.0	2.6
Alcohol use	15.8	3.3
Chronic obstructive pulmonary disease	14.7	3.1
Bipolar disorder	14.1	3.0
Congenital anomalies	13.5	2.9
Osteoarthritis	13.3	2.8
Schizophrenia	12.1	2.6
Obsessive compulsive disorders	10.2	2.2

From Lopez [7], with permission.

To increase the comprehensiveness of the search, it is useful here to include the following textwords: burden of illness, burden of disease, health burden, global burden, quality of life, DALY, mortality, disease cost, sickness cost, and illness cost. A textword search will identify the occurrence of a word or phrase in the title and abstract fields of the citation. She notes that while textword searching, one must be careful to account for variations in spelling and synonyms and to use truncation to identify different endings to terms (e.g., singular vs. plural). Therefore, when using the term ''burden$'' in MEDLINE, the truncation symbol ''$'' means that the search engine would retrieve any citations that contain the words ''burden,'' ''burdens,'' ''burdened,'' and so on.

Searching the current literature about the burden of illness for childhood malaria and pneumonia, she developed the following basic search for MEDLINE using subject headings and textword terms for malaria and pneumonia.

This search resulted in 105 articles from MEDLINE (1998 to July 2003), 88 of which were relevant—much better than what we found ourselves. This allowed us to be reasonably certain that the search strategy has good specificity (so few irrelevant articles will be retrieved)—but what about sensitivity? We'll return to this in a moment.

Database: Ovid MEDLINE

1. exp Malaria/
2. (plasmodium infection$ or malaria).tw.
3. exp Pneumonia/
4. (pulmonary inflammation or lung inflammation or pneumon$).tw
5. or/1-4
6. cost of illness/
7. (burden adj2 (illness or disease$)).tw.
8. ((health or global) adj2 burden).tw.
9. ((disease$ or sickness or illness) adj2 cost$).tw.
10. quality-adjusted life years/
11. (daly or Disability Adjusted Life Year).tw.
12. or/6-11
13. 5 and 12
14. limit 13 to yr=2000-2004
15. limit 14 to all child <0 to 18 years>
16. from 15 keep 8 (105)

This search of MEDLINE was performed using Ovid as an interface. The number in parenthesis in the last line of the search is the number of citations retrieved. The terms with a backslash (/) indicate MeSH terms. Proximity terms like "adj" are used to indicate that one term needs to be near another term. For example, "adj2" indicates that the terms can be up to two words apart anywhere in a title or the abstract of the article.

However, she notes that in the above search she did not add terms for mortality, morbidity, incidence, or prevalence, which are also part of the burden of disease profile. She was concerned that some relevant studies might be missed. Adding in these terms will make the search strategy more inclusive. In the following strategy, she added lines 12 to 16 to include these concepts in the controlled vocabulary and with textword terms.

The retrieval now jumps to 2,426 citations for the same period as the preceding search. If this approach is taken, she suggests that the researcher consider the types of studies that she or he wishes to retrieve. To retrieve studies that focus on literature review articles and health surveys, lines 21 through 25 were added to limit the search:

This reduces the second search set from 2,426 to 295 citations.

She notes that this broader strategy retrieves additional relevant articles that were not included in the first search—and also many citations that were not relevant to the question in this strategy (specificity and precision have fallen)—but, overall, the recall was better (i.e., higher sensitivity, the ability of the search to retrieve all relevant studies).

The bottom line is that from the search outlined above, we were able to reassure ourselves that the WHO Burden of Illness study was by far the most comprehensive and authoritative source for the burden of disease from malaria and acute respiratory infections. Despite the variable quality of the data sources due to which the exact numbers may not be totally accurate, no one contests the high rankings of these conditions. Thus, the case was relatively easy to make by using the World Health Report 2002 material in the introduction to the research proposal.

Database: Ovid MEDLINE

Search strategy:
1. exp Malaria/
2. (plasmodium infection$ or malaria).tw.
3. exp Pneumonia/
4. (pulmonary inflammation or lung inflammation or pneumon$).tw.
5. or/1-4
6. cost of illness/
7. (burden adj2 (illness or disease$)).tw.
8. ((health or global) adj2 burden).tw.
9. ((disease$ or sickness or illness) adj2 cost$).tw.
10. quality-adjusted life years/
11. (daly or Disability Adjusted Life Year).tw.
12. exp Morbidity/
13. exp Mortality/
14. Life Expectancy/
15. (incidence or morbidity or mortality prevalence).tw.
16. mo.fs.
17. or/6-16
18. 5 and 17
19. limit 18 to yr=2000-2004
20. limit 19 to all child <0 to 18 years> (2426)
21. review.pt.
22. review literature.pt.
23. health surveys/
24. or/21-23
25. 20 and 24 (295)

This information is also extremely useful for sample size estimation—for example, two references give the baseline mortality rates for malaria [14] and acute respiratory infections [15] that are needed for calculating the sample size required to detect a 25% reduction in mortality with the appropriate adjustment for a cluster design.

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