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Multidisciplinary Studies of Disease Burden in the Diseases of the Most Impoverished Programme

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ABSTRACT

With limited healthcare resources, rational prioritization of healthcare interventions requires knowledge and analysis of disease burden. In the absence of actual disease-burden data from less-developed countries, various types of morbidity and mortality estimates have been made. Besides having questionable reliability, these estimates do not capture the full burden of a disease since they provide only the number of cases and deaths. The modelling methods that include disability are more comprehensive but are difficult to understand, and their reliability is affected by baseline approximations. To provide policy-makers with information needed for rational decision-making, the Diseases of the Most Impoverished (DOMI) Programme of the International Vaccine Institute has used a multidisciplinary approach to describe the burden of disease due to typhoid fever, shigellosis, and cholera. Recognizing the relative advantages and disadvantages of various methodologies, the programme employs passive clinic-based surveillance in defined communities to provide prospective data. The prospective data are complemented with retrospectively-collected information from existing sources, frequently less accurate and complete but readily available for the whole population over extended periods. To create a more complete picture, economic and qualitative studies specific to each disease are incorporated in these prospective studies. The goal is to achieve a more complete and realistic picture by combining the results of these various methodologies, acknowledging the strengths and limitations of each. These projects also build in-country capacity in terms of treatment, diagnosis, epidemiology, and data management.

Key words: Morbidity; Mortality; Disease burden; Typhoid; Dysentery; Bacillary; Cholera; Vaccines

INTRODUCTION

Immunization is one of the most significant public-health interventions, preventing millions of episodes of infectious diseases and deaths around the world. The bulk of global infectious disease burden is in less-developed countries, where healthcare funds are insufficient. Thus, successful deployment of vaccines to improve health conditions of the poor will depend on careful and continuing analysis of disease burden.

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Disease-burden data, important in many ways, are the basis for rational priority setting of existing resources and mobilization of international support. They are essential for designing sound vaccination strategies, by region, by target age group (e.g. infants, school children, adults), and by epidemiologic scenario (e.g. outbreak response versus prevention of endemic disease). Finally, disease-burden data, such as those on phenotypic distributions of organisms, are crucial for decisions on the types of vaccine to be developed or introduced.

The importance of disease-burden data is highlighted by recent policy-maker surveys, indicating the need for country-specific data. While policy-makers desire more contemporaneous information, it was also apparent that they were not aware of all published and unpublished data for their countries (1).

A general assessment of available estimates

Global statistics are available but these have many limitations. For example, estimates of a single disease from public agencies are often inflated for advocacy purposes. This may be done by presenting the highest among a range of estimated morbidity or mortality figures. This well-meaning intent to draw attention to a specific disease results in a distorted overall global burden. Policy-makers are well aware about the forces at work during the compilation of such estimates of a disease and view this type of information with skepticism.

More comprehensive statistics, based on routine national reporting systems, collected on a regional level, are available from the World Health Organization (WHO) but the accuracy of reporting varies between diseases and across countries (2). Policy-makers are frequently aware of the limitations of data reported to WHO from their own country and often have reservations about these compilations. The estimates are weakened by reliance on routine notification, which may be further weakened by over- and under-diagnosis, incomplete reporting, and delays. Data on specific diseases, such as cholera, may be suppressed due to fear of travel and trade sanctions. Due to limitations on aetiologic diagnosis, some disease categories are too broad to be of use for decisions about specific vaccines, e.g. citation of diarrhoeal diseases *per se*. Furthermore, incidence and mortality rates provide useful information but do not reflect the whole picture. Diseases with relatively low incidence and mortality can cause considerable burden through chronic disability.

Recently, there has been a great deal of interest in measuring the burden of disease in terms of disability-adjusted life years (DALYs). DALYs are the sum of years of life lost due to premature death and years lived with disability of specified severity and duration (3,4). Several parameters are required to calculate DALYs, including age- and gender-specific mortality estimates, incidence of disease estimates, proportion of time individuals are disabled, and severity and duration of disability. A composite measure is created by combining these figures. Two further adjustments are made: discounting and age-weighting. Future years of healthy life lost are discounted by 3% per year, i.e. years in the future count for less compared to those in the present. Discounting future health reduces the relative impact of a childhood death compared to an adult death. The value that is accorded for a year of life lost is also age-weighted, based on the assumption that the relative value of a year

of life rises rapidly from zero at birth to a peak in the early twenties, after which it steadily declines. The strengths of the DALY approach, as a standardized measure of health status, are that it allows comparison between diverse interventions and diverse populations, and it incorporates disability. Its main shortcoming is the uncertainty created by arbitrary value judgements and arm-chair approximations due to lack of information on the severity and duration of actual disability measured in the field (5). Another important drawback is the complexity of the DALY concept, contributing to under-use of DALYs by policy-makers.

To provide easily interpretable country-specific data on incidence, mortality, disability, cost, and perceptions of cholera, typhoid fever, and shigellosis, the Diseases of the Most Impoverished (DOMI) Programme of the International Vaccine Institute is employing multidisciplinary studies in multiple sites (6). DOMI is a programme of research and technical assistance funded by the Bill and Melinda Gates Foundation and designed to accelerate, in a rational fashion, the introduction of new-generation vaccines against cholera, typhoid fever, and shigellosis into programmes for the poor in developing countries. DOMI data are not meant to replace the available statistics on these diseases from other sources but rather to supplement them. In this paper, we review the challenges and strengths of methodologies for assessing disease burden, citing examples from the DOMI Programme and from research on other diseases.

PROSPECTIVE DISEASE-BURDEN STUDIES

When diseases are reliably diagnosed, using appropriate clinical and laboratory methods, and when appropriate medical records for these episodes are archived and made accessible, retrospective studies may be deployed to provide estimates of incidence of treated disease episodes. Unfortunately, routine diagnoses in many developing countries are often made on clinical grounds alone without laboratory confirmation. Medical records in these settings are often not appropriate for use in clinical research. Furthermore, routinely-collected data are not useful for the estimation of disability or economic impact of the illness, e.g. private and institutional costs. For these reasons, special studies of disease burden are often required in developing countries.

In the DOMI Programme, prospective studies have been launched to detect treated cases of cholera, typhoid fever, or shigellosis in defined catchment populations.

The studies measure incidence, disease-specific disability (for typhoid fever and shigellosis), and mortality. When feasible, the surveillance period is two years or more to show year-to-year variation. The studies employ common epidemiologic and microbiologic methods to allow comparison between countries. Currently, the DOMI Programme is conducting prospective studies on cholera in two study areas, typhoid fever in six, and shigellosis in six, with catchment populations ranging from 20,000 to over 200,000. The setting and the age groups under surveillance vary between the sites (Table).

in selected locations, and generalizing their findings to other populations, even within the same country, may be problematic. Thus, study areas should be carefully selected to ensure that they are representative of the population of interest. For some sites, e.g. impoverished slum areas without health centres or rural areas with no laboratories, clinical and diagnostic infrastructure may need to be put in place. However, this substantially increases costs and initially raises questions of feasibility and later sustainability after the surveillance project is completed.

Table. Multi-country prospective study sites of Diseases of the Most Impoverished Programme					
Disease	Location	Local collaborator	Setting	Population	Age group
Cholera	Jakarta, Indonesia	NIHRD US NAMRU-2	Urban (slum)	160,000	All ages
	Kolkata, India	NICED (ICMR)	Urban (slum)	57,000	All ages
Typhoid fever	Hechi, China	CDC, Guangxi province	Urban/rural	110,000	5-60 years
	Karachi, Pakistan	Aga Khan University	Urban (slum)	35,000	2-16 years
	Jakarta, Indonesia	NIHRD US NAMRU-2	Urban (slum)	160,000	All ages
	Hue, Viet Nam	NIHEHue PMC	Urban	70,000	6-18 years
	Kolkata, India	NICED (ICMR)	Urban (slum)	57,000	All ages
	Dhaka, Bangladesh	ICDDR,B	Urban (slum)	20,000	All ages
Shigellosis	Nha Trang, Viet Nam	NIHEKhanh Hoa PMC	Rural	211,000	All ages
	Zhending, China	Fudan University	Rural	97,000	All ages
	Saraburi, Thailand	Mahidol University	Rural	60,000	All ages
	Karachi, Pakistan	Aga Khan University	Urban (slum)	60,000	All ages
	Jakarta, Indonesia	NIHRD US NAMRU-2	Urban (slum)	160,000	All ages
	Dhaka, Bangladesh	ICDDR,B	Urban (slum)	20,000	All ages
	CDC: Centers for Disease Control and Prevention ICDDR,B: Centre for Health and Population Research ICMR: Indian Council of Medical Research NICED: National Institute of Cholera and Enteric Diseases NIHE: National Institute of Hygiene and Epidemiology NIHRD: National Institute of Health Research and Development and Social Welfare PMC: Preventive Medicine Center US NAMRU-2: United States Naval Medical Research Unit No. 2				

Prospective surveillance studies have the advantage of providing a potentially complete and accurate picture of disease burden in a study area, but they are expensive. Much of the costs of the DOMI projects are incurred to ensure in-country capacity in terms of detection, treatment, and diagnosis of the disease, epidemiologic research, and data management. Collaboration with the country's Ministry of Health and/or local academic institutions is a unique feature of the DOMI projects and is undertaken to decrease cost, increase sustainability, and build local capacity.

The basic treatment and laboratory infrastructure required to conduct prospective studies is only available

What surveillance method should be employed?

When conducting prospective studies of disease burden, a major decision is the choice of active versus passive surveillance. Passive surveillance captures cases as they present for healthcare in treatment facilities (7). This method is cost-efficient and generally excludes mild cases that do not require the attention of a health-care worker. To avoid a biased surveillance protocol, an understanding of the community's health-use pattern for the disease of interest is essential. For example, passive, treatment facility-based surveillance will underestimate the burden of a disease for which the study population seeks care with traditional healers. In

addition, healthcare use can be highly variable between clusters within the same study area, indicating that healthcare use is far from homogenous. The population sample sizes should be large enough to prevent these erroneous estimates.

Active surveillance, collecting data to detect the disease of interest by regularly visiting or contacting residents of a community (7), can overcome bias introduced by health-use patterns, since case detection does not depend on treatment choices. However, active surveillance is less suitable for certain conditions, such as diarrhoeal diseases, since the majority of detected episodes will be clinically mild, yet the issue of concern for policies on introducing new vaccines is the burden of severe disease. Active surveillance is labour-intensive and expensive. In addition, field workers require rigorous training and close supervision to ensure adherence to standardized methods. These logistic complexities limit the sample size which can be included in such studies. There is also the danger of fatigue or refusal by the community if the purpose of the study is incompletely understood or if the visits are not conducted in a culturally-acceptable fashion. For these reasons, passive surveillance has been selected over active surveillance for the DOMI Programme, targeting three enteric diseases.

To calculate accurate incidence rates, a reliable baseline census is needed. For study sites in the DOMI Programme where vaccine-effectiveness trials are conducted, censuses of the study community are also repeated annually to ensure a precise denominator and accurate linking of vaccination to outcome. In the DOMI projects, an attempt is made to capture all treated cases from the community, and health-use surveys are incorporated to quantify the proportion of cases captured.

When the burden of disease in a very large population is to be measured and when an estimated (rather than precise) population size as the denominator is adequate, then sentinel surveillance in several secondary or tertiary hospitals may be conducted. Sentinel surveillance is the systematic collection, consolidation, and analysis of data from selected sites, often several hospitals dispersed over a large geographic area. While not being used in the DOMI Programme, sentinel surveillance can be useful for monitoring trends (7).

What aspect of disease should be quantified?

Different surveillance methods measure different entities of the same disease. Many diseases have a broad

spectrum of presentations which may range from sub-clinical to life-threatening. Sentinel surveillance that captures cases in secondary or tertiary hospitals detects more severe forms of the disease than clinic-based community studies. An example is shigellosis for which hospital-based studies showed a relatively frequent occurrence of complications, whereas clinic-based studies do not (8,9). Another example is dengue fever, which is a self-limiting illness, but may progress to its potentially fatal form, dengue haemorrhagic fever. Clinic-based studies could measure the incidence of dengue fever, whereas hospital-based studies would detect mainly the severe forms of the disease (10).

No matter which surveillance method is employed to detect cases, follow-up is necessary to detect deaths and to measure the burden from sequelae when relevant to the disease under study. In the DOMI projects, cases of typhoid fever and shigellosis are followed up for 90 days. For ethical reasons, treatment of the condition and complications need to be assured. Thus, the frequency of complications and the case-fatality rate are likely to be lower than what they would be outside the research setting.

Prospective studies monitoring patients from the time of diagnosis may not be logistically feasible for diseases with long-term disability. To adequately describe the burden of such diseases, retrospective, controlled cohort studies have been employed. This is illustrated by a recent study describing patients admitted to two major paediatric hospitals in Shanghai 6-26 years ago, who were examined by senior neurologists (Zhi-yi Xu. Personal communication, 2004). Three groups were compared in this study: survivors who had confirmed Japanese encephalitis; encephalitic cases who had been admitted with clinical diagnoses of Japanese encephalitis but the diagnosis could not be confirmed by laboratory methods; and a group of normal, neighbourhood controls, matched to the Japanese encephalitis laboratory-confirmed group. The neurologists were blinded with respect to the laboratory results differentiating the first and the second group. The results showed that a major fraction of disease burden from Japanese encephalitis is due to permanent disability, such that the mere number of cases and deaths is inadequate to define the burden of the disease for policy-makers considering introduction of vaccines into their public-health programmes.

How should the disease be diagnosed?

Another conundrum to be faced when conducting studies of the burden of certain diseases is the low sensitivity

of routine diagnostic tests. For example, we are just beginning to appreciate the degree to which culture-confirmed shigellosis underestimates the true disease burden. A real-time polymerase chain reaction technique, which detects the IpaH gene found in all four *Shigella* species, was performed on stool samples from a DOMI disease-burden study in Nha Trang, Viet Nam (11). This PCR technique also detects enteroinvasive *Escherichia coli*, but this organism is thought to be rare in Viet Nam (12). Over 50% and over 30% of culture-negative bloody and non-bloody stools respectively were PCR-positive. Similarly, real-time PCR data on diarrhoeal specimens from a DOMI disease-burden study in Kaeng Koi district, Saraburi province, Thailand, indicate detection rates approximately an order of magnitude higher than those using standard culture methods (Samosornsuk S. Personal communication, 2004). Based on these findings, it is likely that the traditional culture methods probably detect only a fraction of all cases of shigellosis.

As another example, only a proportion of invasive *Haemophilus influenzae* type b (Hib)-associated disease is detectable through cultures of normally sterile body fluids. The effect of this on detected disease burden was illustrated by a trial of the Hib tetanus protein conjugate vaccine in Gambian infants (13). The trial showed that the Hib tetanus protein conjugate vaccine was efficacious not only against culture-positive invasive disease, but also against culture-negative pneumonia, presumably because of insensitivity of cultures in confirming Hib pneumonia (13,14). This highlights the need for better diagnostic methods. In the absence of such methods, especially in less-developed countries, vaccines have been advocated as 'probes' to better define the burden of disease for some pathogens (15).

RETROSPECTIVE STUDIES TO COMPLEMENT PROSPECTIVE STUDIES

The DOMI Programme is conducting a systematic review and abstraction of disease burden of typhoid fever, cholera, and shigellosis between 1991 and 2000 in Bangladesh, China, India, Indonesia, Thailand, Pakistan, and Viet Nam from published and unpublished sources. The project relies mainly on government statistics from routine reporting, representative hospital and laboratory data, and published international and local literature. Disease-specific morbidity and mortality rates are calculated for standardized age groups across countries. Detailed methods and updated output of the study are posted in a specifically designated website (16).

Collating and analyzing the existing data is relatively fast and cheap and may be useful to assess trends and give a nation-wide picture. The data can also be used for selection of a prospective surveillance or vaccine site. However, the data may be incomplete and inaccurate. Data sources and methodologies are frequently poorly defined and highly variable, making comparisons between countries meaningless. Moreover, data can be interpreted merely to fulfil expectations, such as decreasing incidence of certain diseases. Reporting of some diseases may be suppressed due to the fear of trade sanctions. This is particularly true for cholera, a highly political disease, which certain countries report as 'acute, severe diarrhoea' or do not report at all. Due to many weaknesses of using the existing data, it has often been advocated to compare and contrast information from various sources.

SOCIOECONOMIC ASPECTS OF DISEASE-BURDEN STUDIES

Incidence, case-fatality, and disability capture part but not the full essence of disease burden. The DOMI prospective studies provide an opportunity to obtain additional multidisciplinary data needed for policy. These include economic measures of cost-of-illness, socio-behavioural data on community and health providers' perceptions of disease and the need for vaccination, and willingness-to-pay for vaccination. The figure illustrates the multidisciplinary and collaborative nature of the DOMI prospective studies. Many of these surveillance sites are being used or prepared for vaccine trials or demonstration projects. Socioeconomic studies to further assess burden of disease in the DOMI Programme are described below.

Cost-of-illness studies

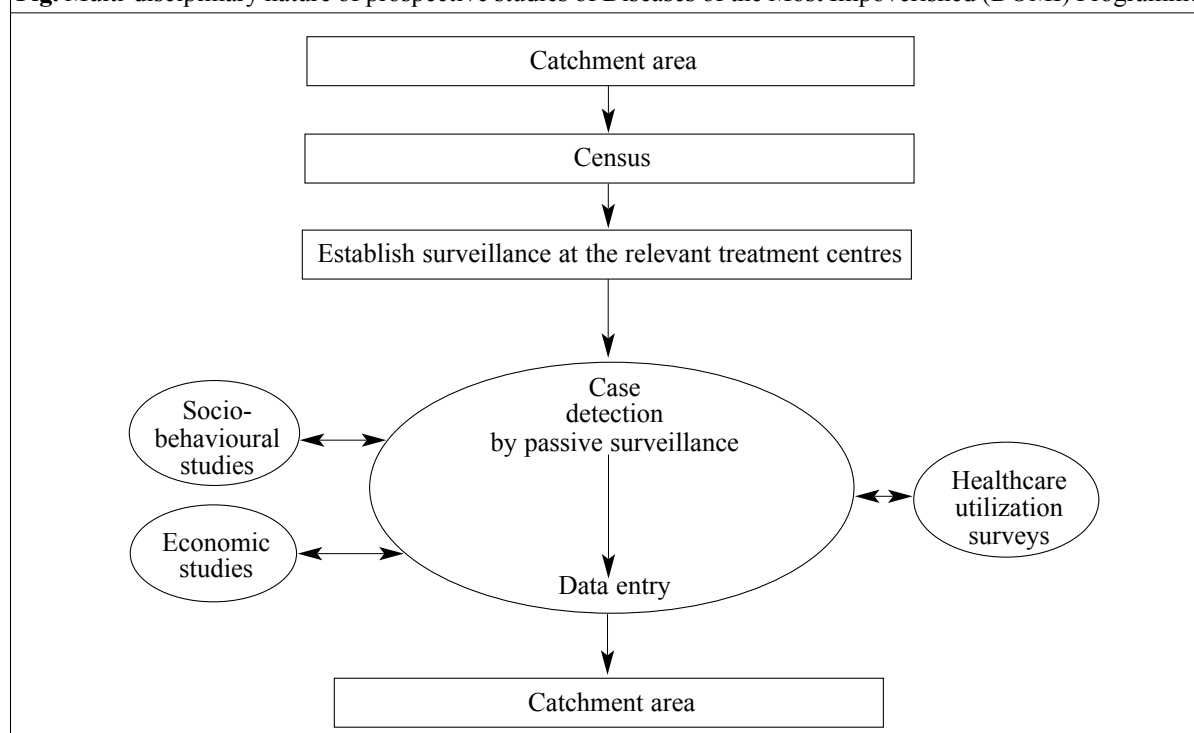
A review of the literature reveals a dearth of data on the real costs of many illnesses targeted by new-generation vaccines. In the DOMI Programme, a series of cost-of-illness studies are being conducted in seven Asian countries. The cases interviewed for the cost-of-illness studies are detected through prospective disease-burden and vaccine-demonstration projects (17). These studies have two components: cost to the patient ('private costs') and cost to the provider ('institutional costs'). Cost to the patient includes both direct, out-of-pocket expenses for consultation fees, drugs, and laboratory tests, and indirect costs, such as loss of productivity, lost wages by patients and caregivers, and cost of temporary household help while a family member is

ill and recuperating. Institutional costs are those associated with diagnosis and treatment of the disease that are borne by the healthcare system rather than by individuals and include time of medical personnel, drugs and supplies, and infrastructure capital for buildings, land, and equipment. Since most DOMI study sites are in slum or poor areas, data collected are representative of costs borne by the poorest segments of society.

Quantitative household surveys

Household surveys are conducted in the DOMI Programme to provide more generalizable data regarding perceptions of disease severity, vulnerability, and causes (19,20). In addition, data are being collected on healthcare use and perceptions of the need and acceptability of an existing vaccine, or, in the case of shigellosis, a

Fig. Multi-disciplinary nature of prospective studies of Diseases of the Most Impoverished (DOMI) Programme



Qualitative research

These studies provide comprehensive qualitative data regarding knowledge, perceptions, and practices regarding the target disease and the associated vaccine (18). The methods include: semi-structured interviews with healthcare providers, community leaders, and residents; case studies of individuals diagnosed with the target diseases; use of 'vignettes' to elicit hypothetical healthcare use for symptoms; community mapping to outline availability of resources; sociocultural calendars to assess regular times of the year when groups of individuals may be more or less able to access healthcare; use of key informants to elucidate and expand information obtained through other methods; and, participant-observation at the research site to further validate findings.

hypothetical target vaccine. These surveys also provide data on logistics information to enhance participation in both vaccine trials and potential future public-health vaccination campaigns. A cross-site framework has been developed for both qualitative and rapid assessment interview guides and household surveys. This framework has been modified for the sociocultural context of each research site using the local expertise and qualitative findings.

CONCLUSION

Policy-makers surveyed in the less-developed world routinely describe the lack of disease-burden data in their countries as a major obstacle to making rational decisions about introducing new vaccines. There is a great need for disease-burden data at the country level.

Recognizing the relative advantages and disadvantages of various methodologies, the DOMI Programme has employed treatment centre-based surveillance in defined communities, as well as prolonged post-discharge follow-up of patients, to provide prospective data on disease incidence, severity, mortality, sequelae and disability. The prospective data are complemented with retrospectively-collected information from the existing sources, frequently less accurate and complete but readily available for the whole population over extended periods. To create a more complete picture, economic and sociobehavioural studies specific to each disease are incorporated in these studies. These include cost-of-illness studies, qualitative research, and quantitative household surveys.

The goal of these studies is to provide information for policy-makers towards accelerating the rational introduction of vaccines against cholera, typhoid fever, and shigellosis. These projects also build in-country capacity in terms of treatment, diagnosis, epidemiologic research, and data management. This multidisciplinary approach to measure the burden of disease could perhaps be applied to other diseases and used for decision-making regarding public-health interventions and control strategies.

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