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6 Issues and Challenges of Public-Health Research in Developing Countries

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KEY POINTS

- There are several aspects of public health research in developing countries that differentiate it from that conducted in more affluent settings, including the need to focus on infectious, perinatal and nutritional disorders especially in children.
- Several methods to assess the burden of and evaluate interventions against infectious diseases are discussed and illustrated with examples.
- Health research in developing countries should comply with current international research standards, so as to assure that the rights, safety and wellbeing of participants are protected and that the study data are credible.
- Public health resources in developing countries are limited. An understanding of the burden of health conditions and the potential impact of interventions and control measures is crucial for rational priority-setting.

Background

Public health is the combination of sciences and skills that aims to protect, promote and restore the wellbeing of a population.[1] Public health research in developing countries is important to quantify health conditions, assess interventions and control measures, as well as inform health policy decisions. There are several aspects of public health research in developing countries that differentiate it from that conducted in more affluent settings.

First, the major health problems in poor populations are infectious, perinatal and nutritional disorders and the highest burden of these problems is found in children. In poor countries, not only are children more vulnerable to disease and death than adults, compared with industrialized nations, they constitute a much larger proportion of the population. Most developing countries have pyramidal populations reflecting high birth rates and short-life spans. By contrast, the age structure of industrialized countries tends to be onion shaped due to decreasing birth rates and longer life expectancy. Recent socioeconomic changes in many poor countries have resulted in a shift in the patterns of disease. As a consequence of lifestyle and behaviour changes, as well as a shift from rural to urban living, developing countries have to cope with chronic noncommunicable illnesses such as adult cardiovascular disease, diabetes and depression, while continuing to struggle with childhood infectious, perinatal and nutritional disorders.[2] Despite these recent developments, the public health sector still tends to focus on children. This is not only because the greatest disease burden still occurs in the youngest age groups, but also because childhood interventions tend to be the most cost-effective and sustainable, and the development of children determines the quality of future populations.

Second, in many parts of sub-Saharan Africa, tropical Asia and Latin America, there is a profound lack of health infrastructure and reliable routinely collected data. Large proportions of births and deaths occur at home and remain unregistered. Many ill patients do not or are unable to seek health care. Treatment facilities are often understaffed and have limited capacity for laboratory-confirmed diagnoses. These factors pose significant challenges for recording accurate morbidity and mortality data. Thus a large fraction of public health research in these settings focuses on health burden assessments to generate the most urgently needed data for public health delivery.

Third, populations in developing countries should be considered as vulnerable in the sense that they have limited financial and political power. It is important that they not be left out of health-related research from which they would benefit, but this research has to be done in accordance with ethical guidelines and principles.

Finally, the bulk of the worldwide disease burden is in developing regions, where only a small fraction of global healthcare funds is available. Epidemiological data are crucial for the rational allocation of these limited resources and to inform decisions about strategies to be implemented. Public health research in developing countries emphasizes the search for cost-effective control and preventive strategies that could potentially benefit large segments of the community rather than expensive treatments for individual patients.

In this chapter, we discuss some important issues and challenges of public-health research in resource-poor settings. This chapter does not cover all aspects of health research in developing countries but will discuss the following: disease burden assessment, outbreak investigation, measuring protection and cost-effectiveness of interventions, good clinical practice in research and using research findings to guide health policy decisions. The focus of all sections will be on infectious diseases.

Methods to Assess the Burden of Infectious Diseases

Improvement of health conditions in a country requires recognition of the main problems, selecting the most appropriate and cost-effective interventions, implementing services efficiently and a continuous assessment of results. On-going analysis of disease burden is essential to the formulation of responsive health policies. There are several epidemiological methods to assess disease burden, the most relevant of which are discussed below.

RETROSPECTIVE REVIEWS OF EXISTING DATA

An assessment of available data provides a general idea about health and disease statistics in a country or region. Collating and analysing existing information is relatively cheap and quick, may be useful to assess trends and may provide a nation- or region-wide picture but its limitations need to be kept in mind. The quality of the assessment depends on the data used to reach it. For example, reliance on public agencies' estimates of a disease, which may be inflated to increase public attention and consequently increase funding, will distort global calculations. The World Health Organization (WHO) compiles more comprehensive health data annually but the accuracy of reporting varies between diseases and across countries.[3] These estimates rely on routine notification, which may be weakened by over- and under-diagnosis, incomplete reporting and delays. Reporting of some diseases may be suppressed due to social taboos (e.g. HIV/AIDS) or the fear of trade sanctions (e.g. cholera).

Systematic reviews and analyses of published and unpublished data on specific diseases may provide more accurate information. For example, Reddy and co-workers conducted a systematic review and meta-analysis of the published literature to assess the burden and the most common aetiologies of community-acquired, non-malaria bloodstream infections in Africa.[4] They found that 13% of adults and 8% of children admitted to hospital with a blood culture taken had a bloodstream infection. The most common isolate was *Salmonella enterica* subspecies (of these, 34% were *S. typhi* and 58% non-typhoidal *Salmonella*) overall in adults and *Streptococcus pneumoniae* in children. Retrospective studies of this nature provide valuable insights for public health planning and research but do not yield detailed and area-specific information. Other limitations include sparse data sources (depending on the health condition of interest) and highly variable or poorly defined methodologies of the original studies. Aside from published findings, there are large amounts of routinely collected and frequently unprocessed disease surveillance reports in health ministries and other institutions. This so-called 'grey literature' may also be included in systematic reviews.

Due to the many weaknesses of using existing data, triangulation of information is recommended, that is comparing and contrasting data from various sources to validate accuracy. Other than WHO publications, peer-reviewed articles and government surveillance reports, innovative sources such as outbreak information from the Program for Monitoring Emerging Diseases (ProMED), which operates as an online forum for infectious disease specialists, microbiologists and public health officials, have also been included in burden of disease assessments.[5]

Traditionally, burden of disease assessments include mortality and morbidity rates, which are useful but do not reflect the total picture. An illness may be uncommon or have low death rates but can still cause considerable burden through chronic disability. In the 1990s, researchers at the Harvard School of Public Health, together with the WHO and the World Bank, estimated the global burden of disease by region and age group, in terms of disability-adjusted life years lost (DALYs). DALYs are the sum of years of life lost due to premature death and years living with disability of specified severity and duration. Using available data from around the world, disease estimates were made for 1990 and mathematical modelling was used to create 5-year projections until 2020.[6] 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. Two further adjustments are made: discounting and age-weighing. Future years of healthy life lost are often 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 child death compared with an adult death. The value that is accorded for a year of life lost is also age-weighed, 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 20s, after which it steadily declines. The strengths of this approach are that it incorporates disability and it allows comparison between diseases, populations and time periods. DALYs are now being used in other types of studies, notably economic analyses (see below). In addition, the WHO is also using a new metric, healthy-adjusted life expectancy (HALE) at birth, which adds up expectation of life for different health states, adjusted for severity distribution, making it sensitive to changes over time or differences between countries in the severity distribution of health states. HALE is defined as the average number of years that a person can expect to live in 'full health' by taking into account years lived in less than full health due to disease and/or injury.

To continue the important work on global health statistics, the Institute for Health Metrics and Evaluation (IHME) was launched at the University of Washington in June 2007 (see: http://www.healthmetricsandevaluation.org). The IHME measures population health status and disease burden, identifies the factors that determine health outcomes and evaluates health policies and interventions. Among their earliest projects were new estimates of mortality rates.

In a separate effort, the Child Health Epidemiology Reference Group of WHO and UNICEF estimated global, regional and national causes of child mortality in 2008.[7] They used multi-cause proportionate mortality models to estimate deaths in neonates and under-5-year-old children and selected single-cause disease models and analysis of available vital registration data to estimate causes of child deaths. They found that of the calculated 8.795 million deaths in children younger than 5 years of age worldwide in 2008, infectious diseases caused 68%, with the largest percentages due to pneumonia, diarrhoea and malaria.

These estimates of global disease burden are useful to guide global programmes and donor assistance, but there are uncertainties about the accuracy of these calculations and the estimates may not be applicable to specific locations. Thus, there remains the continuing need for special field research studies to validate these approximations.

SPECIAL PROSPECTIVE SURVEILLANCE STUDIES

Prospective surveillance studies detect a disease of interest in a cohort to calculate incidence, case fraction, case fatality rate or other measures of frequency. These studies provide data on the risk for illnesses or death in a population but may also be implemented in preparation for intervention trials (see below). Prospective surveillance studies are expensive due to the large costs for case-capture, diagnostic verification, treatment and data management. Frequently, it is necessary to conduct a census to have an accurate and up-to-date denominator. The conduct of

a census requires technical know-how, a large workforce and hence considerable resources.

For some populations without access to treatment facilities or for rural areas with no laboratories, clinical and diagnostic infrastructure may need to be put in place to carry out surveillance studies. This raises questions of feasibility and increases costs substantially. There is also the problem of long-term sustainability after the surveillance project is completed. However, in an impoverished setting without accurate routine reporting of disease, prospective surveillance studies remain the gold standard for providing as complete and accurate a picture of disease burden as possible.

Geographic sites for prospective surveillance studies should be carefully selected to ensure that they are representative of the population of interest. Generalizing findings from one site to other populations, even within the same country, may be problematic. Multi-site studies may be done to assess the burden of disease in a wider regional area. For example, a prospective surveillance study of *Shigella* diarrhoea was undertaken in study sites in six Asian countries (Bangladesh, China, Pakistan, Indonesia, Vietnam and Thailand), to determine disease burden and prevailing species and serotypes.[8] The overall incidence of shigellosis cases presenting for treatment was two episodes per 1000 residents per year in all ages and was highest among children under 5 years old, at 13/1000 per year. The most frequently isolated *Shigella* species was *S. flexneri* in all sites, except in Thailand, where *S. sonnei* was most frequently detected. Findings such as these may be used to guide potential vaccine development or other interventions.

Detection of Cases (Numerator)

A major decision when conducting prospective studies of disease burden is the choice of how and where to detect cases. Active surveillance detects the disease of interest by regularly visiting or contacting residents of a community. Active surveillance is especially appropriate when the disease of interest is characterized by mild symptoms not likely to cause the patient to present for treatment. Active surveillance, particularly if diagnosis requires laboratory testing and confirmation, 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 population size that 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.

Passive surveillance captures cases presenting for care at treatment facilities. Passive surveillance may be done through treatment facilities established by the researchers or through existing primary healthcare units. When the burden of disease in a very large population is to be measured, then sentinel surveillance in several selected secondary or tertiary hospitals dispersed over a large geographic area may be conducted. This method is much more cost-efficient but unlike active surveillance, is subject to potential bias, since case detection is influenced by the study population's utilization of treatment. Although passive surveillance may be enhanced by regular community dialogue and household visits to encourage consultation for the disease of interest, it may still underestimate the burden of a disease for which the population usually self-medicates or seeks care with alternative or traditional healers who do not participate in the study. To avoid this bias, the researchers need to understand the community's utilization of healthcare facilities for the disease of interest and design the surveillance method accordingly.

Information from healthcare utilization surveys may be used to adjust disease estimates obtained through surveillance. For example, in a typhoid fever surveillance study in an urban and rural area in Kenya, Breiman and co-workers used health utilization data to adjust crude incidence rates.[9] The crude and adjusted incidence of blood culture-confirmed typhoid fever in the urban area was 247 and 822 cases per 100 000 person-years of observation (pyo), respectively, compared with 29 and 445 cases per 100 000 pyo in the rural area. The results showed dramatic differences in crude and adjusted, urban and rural typhoid incidence and showed rates similar to those in Asian urban settings, which had not been previously available from Africa.

Many diseases have a wide spectrum of presentations, which can range from sub-clinical to life-threatening. Different surveillance methods may capture different entities of the same disease. Active surveillance tends to detect mild illness; passive clinic-based community studies capture conditions that require a patient to present for care; whereas sentinel surveillance in secondary or tertiary hospitals detects the most severe forms of the disease. For example, dengue, a vector-borne viral illness, has a broad range of presentations. The majority of patients recover following a self-limiting febrile illness but a small proportion progress to severe disease, mostly characterized by plasma leakage leading to circulatory failure.[10] Home visits and clinic-based studies are likely to detect dengue fever, whereas hospital-based studies mainly capture the severe forms of the disease (Figure 6.1). If only a small fraction of cases in the population become severe, several sentinel hospitals in a large surveillance area may be needed in order to detect a sufficient number of patients to reach useful research conclusions about the disease.

Estimation of the Population (Denominator)

To calculate incidence rates (usually in terms of cases per 1000 to 100 000 population per year), the researchers need an accurate estimate of the numerator (the number of cases) as well as the source population from which the cases are captured. The study population may be enumerated through a baseline study census; demographic and healthcare utilization data may also be collected at the same time. If the study aims to determine very precise incidence rates (e.g. in preparation for or during intervention studies), baseline and follow-up censuses to monitor deaths, births and migration during the study period are required. When approximate incidence rates are to be measured, projected population size from the last government census may be sufficient. If the referral base of hospitals included in a sentinel surveillance is unclear, incidence cannot be calculated. Instead, the proportion of the disease of interest among all presentations or admissions (i.e. case fraction) may be reported. This is useful as an indicator of the burden of disease among patients who seek hospital care.

Quantification of Sequelae and Deaths

Quantification of sequelae and deaths may be done through follow-up of cases detected during surveillance or through general mortality surveys. In population-based studies, these are usually reported in terms of sequelae and deaths per 1000 to 100 000 population per year. In hospital-based studies, the

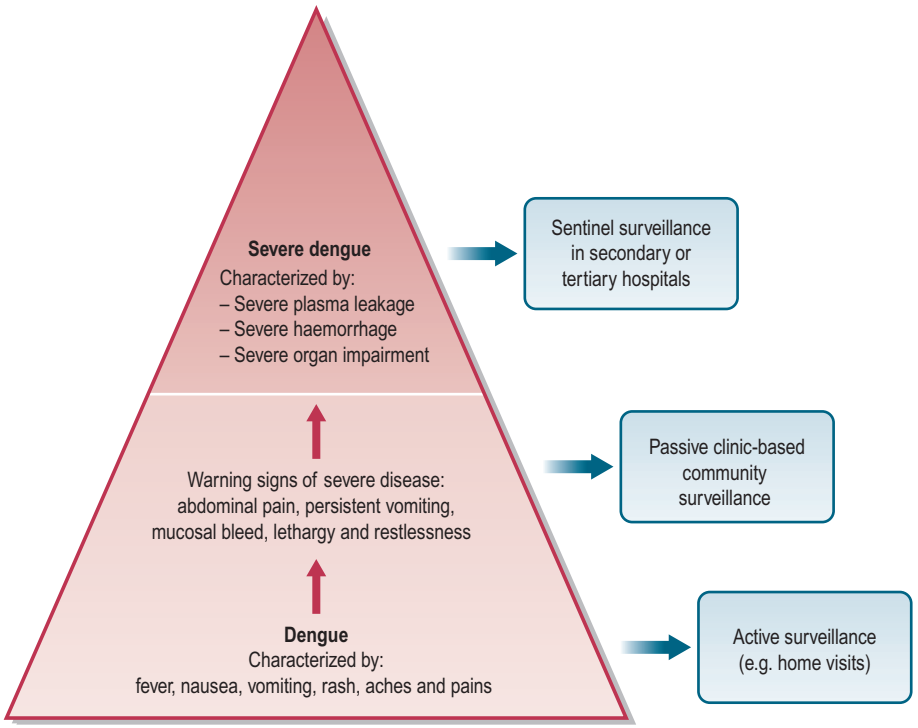

Figure 6.1 The clinical spectrum of dengue related to the surveillance case-capture method. *(Adapted from: WHO. Dengue Guidelines for Diagnosis, Treatment, Prevention and Control. Geneva: World Health Organization; 2009.)*

fraction of presenting or admitted patients who die (case fatality rate) or who develop complications and disability is reported. In prospective surveillance studies, cases have to be immediately and appropriately treated, thus the rates of complications, disability and death are often lower than would be noted outside a research setting. This inherent bias has to be kept in mind when drawing conclusions about sequelae and deaths from prospective research studies.

CROSS-SECTIONAL STUDIES AND CLUSTER SAMPLES

Cross-sectional studies survey a sample of the population at one point in time and estimate the prevalence of a condition, an infection or a disease. The survey tool may be a questionnaire; a physical assessment (e.g. of weight, height or blood pressure); a blood test (e.g. for malaria parasites or HIV infection); or a diagnostic procedure (e.g. chest X-ray). Unlike prospective surveillance studies, cross-sectional surveys do not provide information on incidence, i.e. the number of new cases per population during a specific time period. However, they may provide other important public health information. For example, for diseases that induce life-long antibodies (e.g. HIV, hepatitis A and B), sero-epidemiological studies may show the age groups most affected and when done at different time periods and geographic locations, may indicate the effectiveness of prevention and control strategies. HIV seroprevalence in pregnant women is often used as an indicator of the burden of HIV/AIDS in a community. A major challenge of cross-sectional studies is ensuring that the sample selected and included in the survey is representative of the population of interest.

VERBAL AUTOPSIES

Fatalities in developing countries often go unregistered. Even when death certificates are available and accessible, they may be incomplete or the reported cause of death may be unreliable. Many deaths in developing countries do not occur in hospitals, and officials who had neither treated nor seen the deceased person, may be requested to sign death certificates. Verbal autopsy or verbal postmortem is an alternative method to collect mortality data. It enables investigators to ascribe a probable cause of death, retrospectively. Verbal autopsy consists of a detailed interview of the deceased's next of kin or caregiver and a review of relevant records (e.g. clinic visit records) to determine symptoms and signs of illness before death, so as to establish the most likely cause of death.

There are specific recommendations about the design of verbal autopsies for mortality surveillance.[11] The data collection tool should include structured and unstructured questions; forms for adults and children exist and can be adapted, piloted and validated on-site. The interviewers should be specially trained. The interval between death and interview should be culturally appropriate but not overly long as to affect recall. Algorithms for decoding the completed interviews into causes of death must be clearly pre-defined. For example, two medically trained individuals may independently assess the completed verbal autopsy forms to identify the likely cause of each death. If there is disagreement between the two diagnoses, a third physician may adjudicate the decision. If the physicians cannot determine the cause of death, the death may be recorded as unspecified. Computer-automated methods for assigning cause of death have also been proposed and used. In most studies, the cause of death is assigned according to the International Classification of Diseases, Injuries and Causes of Death codes as recommended by the WHO.[12] Metrics for assessing the performance of different verbal autopsy cause assignment methods have been developed.[13]

Verbal autopsy studies are becoming increasingly common, with the largest to date conducted in India.[14] In this 'One million deaths study', all deaths occurring in 2001–2003 in 1.1 million nationally representative Indian households, were surveyed.

TABLE 6.1 Vaccine Trials Demonstrating Protection against Culture-Proven Invasive Disease, as well as Radiographic Pneumonia

	Vaccine Protection (95% CI) Against	
	Invasive, Culture-Proven Disease	Radiographic Pneumonia
Randomized trial of *Haemophilus influenzae* type-b tetanus protein conjugate for prevention of pneumonia and meningitis in Gambian infants[16]	95% (67–100)	22% (5–35)
Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomized, double-blind, placebo-controlled trial[18]	77% (51–90)	37% (27–45)

Field staff completed verbal autopsies and two of 130 physicians independently assigned a cause to each death. The estimated 1.5 million child deaths in India in 2005 were attributed to five conditions: prematurity/low birth weight, neonatal infections, birth asphyxia/neonatal trauma, diarrhoeal diseases and pneumonia.[15] Each of these can be addressed with known, highly effective and widely practicable interventions.

VACCINE PROBE ASSESSMENTS

In estimating disease burden, the detection of a specific pathogen through diagnostic tests may be a major problem. The best available tests may fail to confirm many cases of illness caused by some pathogens. If a vaccine is highly effective in preventing disease in such undiagnosed syndromes, vaccine trials may be used to 'probe' the burden of disease that has been missed using the available diagnostic tests. For example, only a proportion of invasive *Haemophilus influenzae* type B (Hib)-associated illness is detectable through blood cultures or even more sensitive diagnostic testing, such as polymerase chain reaction. In a large, randomized trial of the Hib-tetanus protein conjugate vaccine in Gambian infants, protection was shown not only against culture-positive invasive disease, but also against culture-negative pneumonia, presumably because of the insensitivity of cultures in confirming Hib-pneumonia.[16,17] This has also been shown in a pneumococcal vaccine trial.[18] Vaccine probe assessments such as these, demonstrate that the burden of some diseases may be much greater than can be proven with the available diagnostic tools (Table 6.1).

Particularly in less-developed countries, where laboratory confirmation of diagnoses may be difficult and where widespread over-the-counter use of antibiotics may result in false-negative diagnoses, highly protective vaccines may be used to probe the total burden of difficult-to-confirm infectious diseases.

SOCIOECONOMIC RESEARCH

The burden of disease in a population may not only be characterized by rates of disease, death and disability; there are also the social impacts and financial costs of illness. The psychosocial consequences of an illness may be evaluated through socio-behavioural studies including rapid and in-depth qualitative surveys, focus group discussions and interviews on knowledge, attitudes and perceptions. For example, in-depth interviews were conducted with 47 children (ages 8–17 years) experiencing the loss of one or both parents due to HIV/AIDS in two rural counties of central China.[19] The majority of the participants reported some level of stigmatization and described feelings of sadness, fear, anxiety, anger, loneliness, low self-esteem, social withdrawal and sleep problems. The results suggested a need for more psychological support and special counselling services, increased public education about HIV/AIDS to decrease discrimination and financial programmes to assist these children.

Rigorous empirical research on the costs of illness is important for rational deployment of strategies to mitigate economic effects. For example, the public, provider and patient costs of culture-confirmed cholera were measured in four cholera-endemic study sites using a combination of hospital- and community-based studies.[20] Families with culture-proven cases were surveyed at home, 7 and 14 days after confirmation of illness. Hospital-based studies found that the costs of severe cholera were US$32 and US$47 in Matlab (Bangladesh) and Beira (Mozambique), respectively. Community-based studies in North Jakarta (Indonesia) and Kolkata (India) found that cholera cases cost between US$28 and US$206, depending on hospitalization. Patients' cost of illness, as a percentage of average monthly income, was 21% and 65% for hospitalized cases in Kolkata and North Jakarta, respectively. This analysis highlighted the financial burden of an acute diarrhoeal disease on households, often contributing to further poverty. The impact of chronic conditions such as HIV/AIDS on individuals, households and countries is more difficult to quantify. Presumably, HIV/AIDS is an important cause of poverty in many parts of sub-Saharan Africa. And yet, the impoverishing effects of AIDS have been inadequately assessed by existing studies, likely because of methodological challenges.[21]

Policy-maker surveys may be conducted to elicit government opinions about diseases. For example, DeRoeck and co-workers interviewed policy-makers and other influential professionals in four South-east Asian countries (Cambodia, Indonesia, Philippines and Vietnam) to determine their views on the public health importance of dengue, the need for a vaccine and the determinants influencing its potential introduction.[22]

OUTBREAK INVESTIGATIONS

An outbreak is the occurrence of disease episodes in greater numbers than would be expected at a particular time and place. The population at risk may range from a small, localized group to large populations. Infectious disease pathogens may cause epidemics that affect regional areas or pandemics that spread around the world. Recently, outbreak investigation and response have received unprecedented prominence with the severe acute respiratory syndrome (SARS) epidemic and the influenza A (H1N1) pandemic.

Once a report of an outbreak is received, there are several steps in its investigation.[23] Specimens are collected for laboratory verification of the diagnosis. Researchers develop a clinical case

definition. Using this definition, cases and deaths are identified and the outbreak is analysed by time, place and person. Starting with the first case identified (index case), the number of cases by day or week is plotted to create an outbreak curve. Cases may be mapped and affected persons described in terms of age, sex and other relevant characteristics. Prevention and control procedures are implemented as soon as possible. Treatment centres may be set-up, guidelines for management disseminated and supplies and other logistics provided.

There are several outbreak patterns, each associated with a distinctive epidemic curve. In a common source outbreak, cases acquire the infection from the same source (e.g. a contaminated water supply). This may be a point source outbreak when the exposure occurs in less than one incubation period or a continuous source outbreak when the exposure occurs over multiple incubation periods. In a propagated outbreak, the pathogen is transmitted from person to person.

It is important to determine how the disease is transmitted in an outbreak, so that interventions can be taken to stop the current epidemic and to prevent future epidemics. A cohort study or a case–control study may be conducted to identify the risk factors that would cause an individual to become ill with the disease causing the outbreak. Cohort studies work best for well-defined populations (e.g. an outbreak that occurs among people who attended a gathering such as a funeral), while case–control studies work best for outbreaks where the population is not well-defined. The decision regarding the type of study that would be appropriate to investigate an outbreak also rests on the magnitude of risk, the latency of exposure to disease, the prevalence of exposure and timing (i.e. in some instances, it may be too late to conduct a cohort study).

Evaluation of Interventions against Infectious Disease

An intervention refers to an intentional change in some aspect of the individual.[1] Public health interventions against infectious diseases are varied and may range from behavioural (e.g. the promotion of hand-washing and breast-feeding; distribution of condoms to control the spread of sexually transmitted diseases; deployment of insecticide-treated bed nets to prevent malaria); structural (e.g. improvement of water supply and sanitation); to pharmacological (vaccine or drug administration). Rational policy-making in developing countries includes the evaluation of potential interventions in terms of safety, efficacy, effectiveness and financial impact.

The protection afforded by many traditional interventions may be widely known and accepted, while that from newer strategies may need to be evaluated. In the assessment of both pharmacological and non-pharmacological interventions, these need to be carried out under ethical conditions and using robust study designs so as to reach valid conclusions. The evaluation of pharmacological compared to non-pharmacological interventions is more stringent; candidate drugs and vaccines require a very careful, phased approach to minimize the potential risks to participants in trials.[24] If there is an intention to license these drugs or vaccines, regulatory agencies (e.g. the US Food and Drug Administration or the equivalent National Regulatory Agency in a developing country) scrutinize the findings of each step in this process.

RANDOMIZED CONTROLLED TRIALS

The randomized controlled trial (RCT) is the gold standard method for evaluating the efficacy of an intervention. The method involves randomly allocating participants into study and control groups, to receive or not receive the intervention being evaluated.[1] The results are assessed by a comparison of rates of disease or other appropriate outcome in the study and control group.

There are practical challenges to doing RCTs in less developed countries, where infrastructure and expertise may not be available. But many infections are geographically limited to developing countries and data on protection against naturally occurring disease can only be obtained in these sites. Even for diseases occurring in both industrialized and developing countries, study results may not necessarily be generalizable because of differences in population characteristics. For example, it has been shown that the immunogenicity of vaccines can be much lower in populations in developing compared with industrialized countries. Poorer performance has been especially problematic for orally administered live vaccines. The efficacy of the Rotarix™ and RotaTeq™ vaccines against severe rotavirus related disease in developing countries of Asia, Africa, and Central America does not appear to be as high as that seen in developed countries.[25–27] Another frequently cited example is the finding that three doses of oral polio vaccine, as formerly used in the USA, resulted in sustained, probably lifelong immunity, whereas many children in developing countries may require >3 doses for adequate seroconversion.[28] The poor performance of these vaccines in developing country populations is not well understood, but could be due to several factors, including high levels of pre-existing natural immunity (either maternal or infection-derived), poor nutritional status, tropical enteropathy and co-existing infections.[29]

Even within the developing world, findings from a randomized, controlled trial done in one region may not be generalizable to another region because of differences in the epidemiology of disease. For example, to seek new and improved treatments for severe falciparum malaria, a large multinational randomized comparison of parenteral artesunate versus the standard therapy of parenteral quinine was conducted in South-east Asia.[30] The trial proved that severe falciparum malaria mortality could be reduced by 30% in Asian adults when artesunate is used, but key decision-makers in Africa felt the results of this study were not generalizable to their populations where severe *falciparum* malaria tends to occur in children, rather than in adults. Over a 5 year period 5000 children with severe malaria in nine African countries participated in a large, multicentre, open-label randomized trial that established the superior efficacy of parenteral artesunate over quinine and led to a change in treatment guidelines.[31,32]

EFFICACY VERSUS EFFECTIVENESS

Conventional efficacy studies focus on the performance of interventions under ideal conditions whereas effectiveness trials address the protection afforded by interventions under real public health conditions.[33] Evidence from efficacy trials may not suffice to convince policymakers to allocate limited resources for new interventions. Effectiveness studies of licensed drugs and vaccines may be conducted in developing countries to collect evidence on feasibility, acceptability, and practical

impact or effectiveness. For example, an effectiveness trial of the typhoid Vi vaccine was conducted to provide evidence for wider-scale implementation.[34] Slum-dwelling residents of Kolkata, India, who were 2 years of age or older were randomly assigned to receive a single dose of either Vi vaccine or inactivated hepatitis A vaccine, according to geographic clusters, and were followed for 2 years. The level of protective effectiveness was 61%. Interestingly, the design of the trial also allowed assessment of the protection of unvaccinated neighbours of vaccinated persons. This indirect protection was estimated at 44%. Not only the direct but also the indirect protection by Vi vaccine should be considered in future deliberations about introducing this vaccine in typhoid fever endemic areas.

OTHER DESIGNS

Other than randomized controlled trials, observational studies such as cohort, household contact, case–control, screening and case-cohort studies may be used to assess the effectiveness of an intervention.[35] Since the intervention is not randomly allocated in observational studies, bias is unavoidable. But it may still be possible to obtain sufficiently good estimates of protection from observational studies for public health purposes. Potential biases should be considered in the design phase and steps taken to minimize them if possible. As many more new and innovative interventions become available and the costs of randomized controlled trials escalate, the role of observational methods will become even more important.

ANALYSES OF ECONOMIC IMPACT

The economic impact of an intervention may be assessed using various methods; all of which weigh the costs of an illness with the expenditure for and benefits from an intervention (Figure 6.2). A cost–benefit analysis expresses costs and benefits in terms of money,[36] but monetary value may not be appropriate nor completely capture the benefits from health interventions.

In cost-effectiveness analysis, the cost of the intervention is also measured in monetary units but the benefit gained is expressed in terms of cases, deaths and DALYs averted. For example, in conjunction with the typhoid Vi vaccine effectiveness trial cited above, the cost-effectiveness of vaccination programmes in endemic sites in Asia was calculated.[37] It was estimated that a programme targeting all children ages 2–15 years old would prevent 456, 158 and 258 typhoid cases (and 4.6, 1.6 and 2.6 deaths), and avert 126, 44 and 72 DALYs over 3 years in Kolkata, North Jakarta and Karachi, respectively. The cost was calculated at US$160 and US$549, per DALY averted in Kolkata (India) and North Jakarta (Indonesia), respectively, and considered very cost-effective.

Cost-effective analyses may also compare two or more intervention options. For example, in association with the clinical trial of children with severe malaria in sub-Saharan Africa discussed above,[31] the cost-effectiveness of parenteral artesunate and quinine was compared. The mean cost of treating severe malaria patients was similar in the two study groups: US$63.5 in the quinine and US$66.5 in the artesunate arm. Compared with quinine as a baseline, artesunate showed an incremental cost of US$3.8 per DALY averted and an incremental cost per death averted of US$123. Artesunate was determined to be a highly cost-effective and affordable alternative to quinine for treating children with severe malaria.[38]

Cost-utility analysis estimate the ratio between the cost of a health-related intervention and the benefit it produces in terms of quality-adjusted number of years lived by the beneficiaries. A common metric in the denominator allows comparisons of diverse interventions against diverse diseases. An example is the use of DALYs.

Cost-benefit, cost-effective and cost-utility analyses do not incorporate the populations' stated preferences in decisions to finance new interventions. During the past 20 years, several stated preference studies have been conducted in less-developed countries, some of which have assessed willingness-to-pay for various public health interventions.[39] In general, the studies have shown low willingness to pay for these interventions, which is not surprising considering the competing priorities for food, shelter and other basic necessities. Thus, in the poor regions of the world, local governments and international donors have the obligation to continue to provide and implement much needed interventions.

Good Clinical Practice and Ethical Issues

Health research in developing countries should comply with current international research standards, so as to assure that the rights, safety and wellbeing of participants are protected

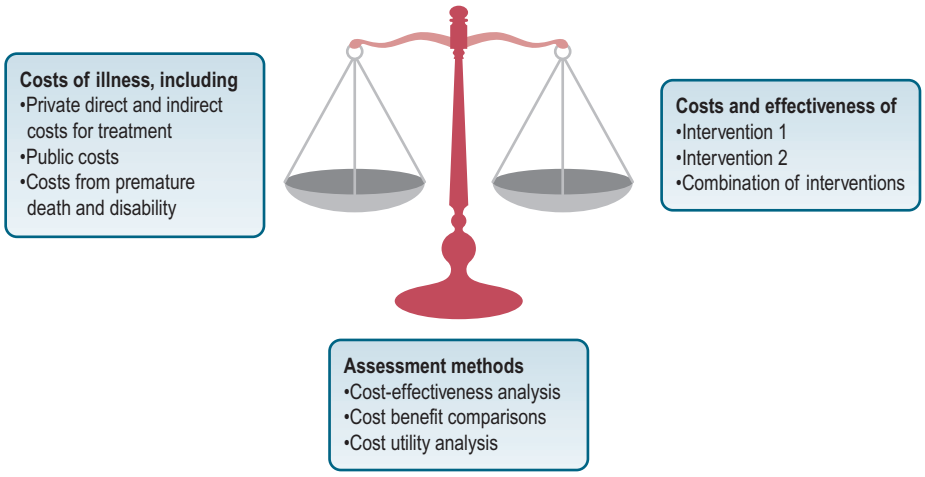

Figure 6.2 Evaluating the economic impact of an intervention.

and that the study data are credible. The ethics of research in developing countries has been the subject of intense discussion.[40] Issues being deliberated include: choosing the appropriate research question and design; use of placebo control groups in randomised controlled trials; capacity-building of local ethics committees to ensure sound and appropriate local review of the study protocol; ensuring that informed consent and assent is obtained which may be especially challenging in impoverished and less educated populations; the potential coerciveness of the offer to participate in research in locations where this may be the only means of obtaining health care; providing equal consideration to participants (including children and pregnant women) in research that would yield results beneficial to them while ensuring the protection of vulnerable participants; ensuring equal distribution of the burden and benefits of the research and minimizing the risk to participants.[41] These concerns are consistent with principles embraced in the World Medical Association's 'Helsinki Declaration' from 1964 and most recently amended in 2008. Special and continuing vigilance is necessary to safeguard the rights of populations in developing countries.

Although general ethical principles apply to all types of research, Good Clinical Practice (GCP) guidelines developed by the International Conference on Harmonization[42] are the standard for conduct of clinical research for licensure of pharmacologic interventions (e.g. vaccine and drugs). The GCP guidelines aim to ensure not only ethical conduct of studies, but generation of credible data. The guidelines' objectives of documenting informed consent, participant safety and data integrity are worthy. However, it has been argued that these GCP guidelines are based on consensus of expert opinions and not on evidence.[43] Not surprisingly, the individual standards as well as the concept of standardization of clinical trials of pharmacological interventions are not free of controversy. There have been increasing calls for the guidelines to be made more scientific, up-to-date, flexible and simple through collaborative and evidence-based efforts.[43,44] For trials in developing countries, rigid adherence to GCP standards as they are now formulated, have both positive and unfavorable consequences.[45] The complexity and expense of clinical trials has risen rapidly in recent years. A portion of this increased expense arises from the extensive documentation and auditing requirements demanded by GCP guidelines. This constitutes a disincentive to the clinical testing of drugs and vaccines for diseases mainly affecting developing countries and for which profitable markets are not foreseen. Furthermore, compliance with the stringent GCP requirements often requires the engagement of expensive contract research organizations, which are, in some cases, highly lucrative publicly traded enterprises. On the other hand, funders are increasingly demanding adherence to GCP and it is unlikely that regulatory agencies will license a new product without the diligence assured by a contract research organization.

Use of Health Research Findings to Guide Health Policy Decisions

We live in an era in which only a fraction of useful health interventions for populations in developing countries are delivered to these populations. This is true both for interventions that are well established as well as for new interventions. There are many reasons. Perhaps the most obvious obstacle is financial, with highly constrained healthcare budgets in developing countries and limited pools of donor resources being inadequate to fund all potentially useful interventions. Because of financial constraints, policy-makers at the global, regional and national levels increasingly demand hard evidence to compare the potential value of alternative interventions and to justify the expenditure of resources to fund the introduction of interventions.

Provision of data on the burden of the disease(s) targeted by the intervention is the most common kind of evidence requested by policy-makers. Evidence about the efficacy of an intervention, often obtained from rigorous clinical trials, is usually also needed. Even for interventions that appear attractive in evaluations of efficacy, there may be uncertainties about the logistic and programmatic feasibility of implementation in public health programmes, as well as about the impact upon desired health outcomes under real-life, public health conditions. Thus, evidence about intervention effectiveness is also relevant to policy deliberations. And, as alluded to above, policy-makers typically require evidence of cost-effectiveness of interventions, ideally expressed as the net cost per DALY averted in order to compare interventions for different diseases, as well as prophylactic versus therapeutic interventions.

Finally, it may be helpful to have an indication of the population demand for the intervention, even including assessment of willingness to pay for the intervention. Table 6.2 provides an outline of a programme of translational research (sometimes called 'implementation research') of this sort used in the Diseases of the Most Impoverished (DOMI) Program – a programme funded by the Bill & Melinda Gates Foundation to accelerate the introduction of new-generation vaccines against cholera, typhoid and shigellosis – for the introduction of killed oral cholera vaccines in several countries of Asia and Africa.[46]

TABLE 6.2 Multidisciplinary, Multi-Country Studies of The 'DOMI Program' to Provide Evidence to Inform Policy on the Introduction of Killed, Oral Cholera Vaccines

	Country						
Type of Activity	Bangladesh	China	India	Indonesia	Mozambique	Pakistan	Vietnam
Prospective disease burden studies	+		+	+	+	+	+
Meta-analysis of disease burden	+	+	+	+		+	+
Cost of illness studies	+		+	+	+		+
Assessment of feasibility, acceptability and impact	+		+		+		+
Cost of delivery studies	+		+		+		+
Cost-effectiveness analyses	+		+	+	+		+
Assessment of demand/willingness to pay studies	+	+	+	+	+	+	+
Policy analyses	+	+	+	+	+	+	+

While the ensemble of evidence generated by the DOMI Program has now become relatively standard in programmes to generate policy-relevant evidence on interventions for developing countries, it is important to note that several additional strategies are helpful if such evidence is to influence or support policy. Programmes to generate evidence should be formulated and conducted in partnership with policy-makers and healthcare professionals in the countries where the intervention is being contemplated for introduction. For example, the DOMI Program was based on an initial systematic survey of policy-makers about evidence needs in targeted countries, and the DOMI field research programme was formulated on the basis of these findings.[47] Also, DOMI's multifaceted research programme to generate evidence was implemented in partnership with Ministries of Health in order to ensure that the decision-makers would have a sense of ownership of the findings. Moreover, if the evidence is to have an impact at the regional and global levels, as well as the national level, it may be helpful to construct multi-country programmes of research, with study designs and procedures standardized across countries. As shown in Table 6.2, the DOMI Program employed a standardized, multi-country approach to its studies, to generate evidence to inform policy on the introduction of killed oral cholera vaccines. This led to an evidence base that provided interpretable comparative data across countries.

Beyond generating the data, packaging and presentation of the evidence in a way that is convincing for policy-makers is of critical importance if the evidence is to have an impact on policy. This may require development of both detailed 'investment cases', as well as much shorter policy briefs. Presentation of the information in scientific journals is important, but it is also important to arrange presentations of study findings in both small and large meetings attended by policy-makers. The onus of assuring the attendance of policy-makers at such meetings is on the investigators. Finally, because the WHO has the ear of policy-makers, presentation of the findings at relevant WHO meetings, at both the regional and global levels is critical. An illustration of this approach was provided by efforts to synthesize and communicate the evidence on cholera and oral cholera vaccines. Synthesis of these findings into a white paper, and subsequently an investment case, for WHO's Scientific Advisory Group of Experts led to a greatly strengthened recommendation on oral cholera vaccines by WHO,[48] and provided the background for a recent World Health Assembly resolution, recommending the use of vaccines in the public health armamentarium against cholera.[49]

Summary

Public health research in developing country populations is complicated and challenging, but necessary. When conducted in a well-planned and focused manner, it can yield many important gains including understanding health problems better, informing policy decisions and rational deployment of interventions resulting in large health benefits.

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