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The child health epidemiology reference group reviews of the effectiveness of interventions to reduce maternal, neonatal and child mortality

Cynthia Boschi-Pinto,[1] Mark Young[2] and Robert E Black[3]*

[1]Department of Child and Adolescent Health and Development, World Health Organization, Geneva, Switzerland,
[2]Programme Division, United Nations Children's Fund, New York, NY, USA and
[3]Department of International Health, The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA.

*Corresponding author. Department of International Health, The Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, Baltimore, MD 21205, USA. Email: rblack@jhsph.edu

Introduction

This article consists of a short introduction to the reviews presented in this series. It focuses on the contribution of the work of the Child Health Epidemiology Reference Group (CHERG) to the Lives Saved Tool (*LiST*) through the development of estimates of key inputs to the model. These include previously estimated country-specific distribution of the main causes of under-5 deaths and of the proportion of these deaths that can be averted by specific interventions (affected fraction), along with the newly estimated efficacy/effectiveness of child survival interventions that are presented in detail in individual papers in this volume. This series reflects our efforts to make all data, materials and methods used in the estimation of parameters fully available and transparent.

The CHERG

The CHERG was established by the World Health Organization (WHO) in 2001 to address the inadequacy of existing data and methods and the difficulty in documenting progress and identifying gaps in child health epidemiology. The CHERG has established itself as a unique source for independent technical work that responds to the main epidemiological questions in child health. It is composed of international experts that are external to and independent from the UN system. The main initial objectives of the group were: (i) to provide global technical leadership in the development and improvement of epidemiological estimates for children under five, particularly regarding cause-specific morbidity and mortality; (ii) to address general methodological issues; and (iii) to assess the potential contribution and impact of interventions to reduce under-5 mortality. The group's working method usually starts by convening small technical working groups to address key questions; by conducting extensive systematic reviews, analyses and modelling to develop estimates; and assembling regular meetings that involve the lead scientists from the groups. These meetings are convened by WHO and UNICEF and occur approximately every six months to define future work and report on progress and also to provide peer review, thus ensuring high quality and transparency.

CHERG's primary mandate was to review and improve data collection, methods and assumptions underlying estimates of the cause-specific distribution of deaths due to the major causes of child mortality worldwide: causes of death in the first 28 days of life (neonatal causes); pneumonia; diarrhoea; malaria; and measles.[1–6] CHERG has also provided estimates of important childhood morbidities such as pneumonia[7,8] and malaria.[9] In addition, substantial new information on etiology has become available in 2009.[10–12] More recently, a thorough re-examination of previous reviews[13,14] on the effectiveness of different child survival interventions has been carried out by CHERG working groups and is presented in detail in this series.

The Lives Saved Tool (*LiST*)

The over-arching goal of the *LiST* is to promote evidence-based decision making for planning the appropriate expansion of maternal, neonatal and child health interventions and to estimate costs and budget requirements for their implementation in low-income countries. Its main objectives are to

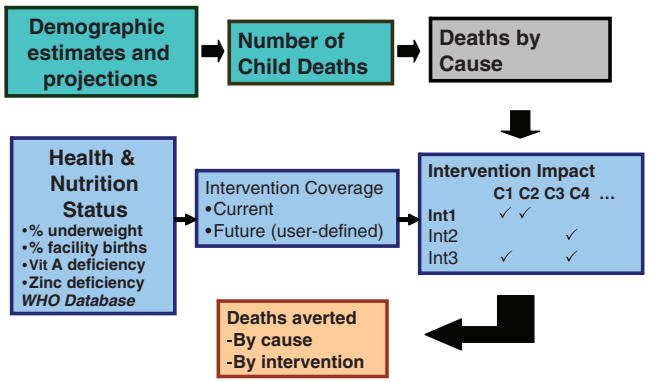

Figure 1 Inputs to the *LiST* tool and schematic flow
Source: Stover J. Presentation given at the CHERG meeting in June 2008

estimate the number of lives saved when scaling up key interventions and to provide a user-friendly tool for child survival planning in developing countries.[15] The tool was developed within the Spectrum software package and the model enclosed in it is expected to facilitate the assessment of the impact of different scenarios when expanding the coverage of different interventions, cost these scenarios and make judgements on the cost-effectiveness of different courses of action.[15]

The *LiST* draws on various sources of country-specific information such as demographic and socio-economic information; total number of child deaths; their distribution by cause, health and nutrition statuses, present and future (user-defined) coverage of key child survival interventions and their estimated efficacies and/or effectiveness by cause of death; and the proportion of deaths that can be averted by a specific intervention (or the affected fraction). Information on interventions, cause-of-death profiles and coverage assumptions have been generated from the work of WHO and UNICEF, often through the CHERG. Using this set of information, the model currently enables the estimation of the number of deaths that would be averted if specific interventions had their coverage expanded. Figure 1 shows a diagram with inputs needed to the model and their schematic flow.

CHERG and *LiST*

In the last few years, there have been major advances in gathering key information needed for planning at the country level. As part of its ongoing work on reviewing and documenting child health information, the CHERG and its partners have been collaborating with the *LiST* project by providing estimates for three of the five key parameters used in the tool model: 'causes of death, affected fractions and impact of interventions'.

Causes of death included in the model consist of: pneumonia, diarrhoea, malaria, measles, AIDS and neonatal causes of mortality (prematurity, birth asphyxia, severe infections, tetanus, congenital anomalies and diarrhoea). Low birth weight and stunting are treated as contributory factors to the above-mentioned causes of death. The cohort approach used in the model allows for specific nutritional factors to contribute deaths in different periods of life. For example, intrauterine growth restriction contributes to deaths not only in the neonatal period, but also, via stunting, in subsequent periods of a child's life cycle. In these subsequent periods, stunting is impacted by infant and child nutrition interventions. The cause-of-death estimation process carried out by the CHERG involved the undertaking of systematic, extensive and comprehensive literature reviews of published studies and the development of a methodological approach that is transparent and consistent across different diseases. Details of the estimation process have been described elsewhere.[2,3]

The proportion of deaths that can be averted by specific interventions such as vaccines has also been estimated. Rotavirus vaccine, for example, can only avert diarrhoea deaths that are due to Rotavirus; therefore, its estimated effectiveness can only be applied to this 'fraction' of diarrhoea deaths. Similarly, Hib and Pneumococcal vaccines can only avert those pneumonia deaths that are due to *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae,* respectively. The proportion of diarrhoea deaths due to Rotavirus and of pneumonia deaths due to Hib and to pneumococcus have been estimated by CHERG and its partners.[10–12]

The main focus of this series, however, is on the CHERG's process for estimating the impact of key childhood interventions on the survival of children younger than five years of age. The main goal of the reviews presented in this series is to estimate the magnitude of the effect of the intervention on a specific cause of death. In order to achieve this objective, we first established criteria for the inclusion of interventions in the tool, based on two axes: 'the likely impact of the intervention and the evidence of its effect'. The first criteria determined the inclusion of (i) interventions that are likely to have an impact on a cause of death that is relevant in at least some settings (e.g. areas with high malaria or HIV burden); and (ii) interventions that are not likely to have an impact on mortality because of its current high coverage, but that would probably result in an increase of mortality where coverage levels are not sustained (e.g. measles and DPT vaccines). The criteria based on evidence of effectiveness established that, to be included in the tool, the intervention should have (i) at least some documented evidence of a direct effect on cause-specific mortality, on all cause mortality or on severe morbidity or (ii) a higher level of evidence of a direct effect on mild/moderate morbidity or (iii) clear and indubitable clinical benefit (e.g. C-section for obstructed labour or foetal distress and antibiotics for infection).

Once we defined which interventions should be part of the *LiST,* we started the process to estimate the magnitude of their effect on specific causes of death. The first step consisted of a Cochrane-type systematic literature review using at least PubMed, Cochrane reviews and the WHO Regional Databases. Whenever Cochrane reviews were used, these were revisited and reappraised, meaning that studies were reassessed or reviewed yet again. For many interventions, the evidence for an effect on cause-specific mortality was fairly weak, requiring therefore more in-depth literature searches on different study designs and/or on outcomes other than mortality. Because the specific aim of the reviews was to estimate the effect of an intervention on cause-specific mortality, the CHERG developed a series of rules for combining limited cause-specific mortality data with all-cause mortality, serious morbidity and moderate morbidity data in order to estimate the final effect (and uncertainty bounds) of each intervention in reducing cause-specific mortality. These rules are presented in detail by Cousens *et al*.[16] The final combined estimates will be those used as input to the *LiST* of the effect of increased coverage of a specific intervention on cause-specific mortality and thus the number of lives saved by scaling up such an intervention.

The CHERG developed a standardized abstraction table for use across all technical groups and all interventions in which information on the main characteristics of the studies retained for analysis were abstracted and presented. Such information comprise: (i) study identifiers and context such as author, year of publication, journal reference, country where and year when the study was carried out, etc; (ii) characteristics of study design and assessment of its limitations; (iii) characteristics of the intervention in the specific study (definition, delivery channel, target population, etc); (iv) definition of outcome (under-5 mortality, neonatal mortality, morbidity, etc) and impact of intervention on study-specific outcome; and (v) summary of characteristics, including overall study limitations and evaluation of the directness of the effect on studied outcome in relation to the outcome of interest.

Meta-analyses were then performed for each outcome and by each type of study design as appropriate. Whenever the evidence for an effect on cause-specific mortality was identified to be weak, a series of assumptions had to be made,[17] which resulted in more complex and stringent methods than standard randomized control trials pooled- or meta-analyses and in more conservative effect estimates.

The last step of the review process was the application of the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[17] The GRADE approach assesses the risk of bias in individual studies as well as the quality of the assembled evidence on the effect of each intervention on the outcome of interest. The latter is classified as high, moderate, low or very low. For example, randomized trials are initially categorized as high quality but can be downgraded; similarly, observational studies can be upgraded. Factors that decrease the quality of evidence include limitations in design, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results, or high probability of publication bias. Factors that can increase the quality level of a body of evidence include large magnitude of effect, if all plausible confounding would reduce a demonstrated effect and a dose-response gradient. Final assessment of the overall quality of evidence and a summary of its GRADE appraisal are presented in each individual paper in a pre-defined table format.

CHERG and *LiST*: uniting efforts for the achievement of MDG4

It has been estimated that universal coverage of available interventions could prevent about two-thirds of childhood deaths.[13] Some recent analysis provided further evidence that increases in coverage of key interventions are associated with reductions in under-5 mortality.[18] Consequently, specific efforts for improving coverage of these key interventions is a possible means for health programmes to contribute to the achievement of the Millennium Development Goal 4 (MDG4).

The CHERG and *LiST* projects share the common objective of providing policy makers with the best available evidence that will enable informed decisions to be made regarding maternal, neonatal and child survival. Our ultimate goal is that the information provided through this new tool will be used for planning purposes in countries and districts; more specifically, helping to define what interventions are most needed and to guide the introduction and scaling up of strategic interventions. An integrated and user-friendly tool for use by countries has the potential to facilitate:

(i) evidence-based policy guidance
(ii) results-based strategies and plans for maternal, newborn and child survival programmes and
(iii) inputs for sector budgets and medium term expenditure frameworks (MTEFs)

In conclusion, this common effort should provide the necessary support, encouragement and opportunity to help policy makers and programme managers in countries, and donors and international agencies to set clear coverage targets, implement effective strategies and monitor progress of their achievement.

Future plans for joint CHERG-*LiST* work

Work is underway to also include in *LiST* costing modules and estimated impact of interventions on

maternal mortality and on stillbirths. Links to existing costing tools such as the World Bank and UNICEF's Marginal Budgeting for Bottleneck (MBB) tool and the WHO supported costing tool for child survival are being developed and will allow the estimation of costs for scenarios of increased coverage generated by *LiST*. The approach to estimating the impact of interventions on maternal mortality and stillbirths is very similar to that used for child mortality. For each country, causes and levels of maternal deaths and stillbirths have been defined. Evidence is also being collected on the effects of interventions that have an impact on these two outcomes yielding estimates of the reduction in maternal deaths and stillbirths with the scaling up of these interventions. This work is currently being carried out within the CHERG, but has also strong links with groups that have a greater focus on stillbirths such as GAPPS. The most recent version of *LiST* along with documentation and training materials can be viewed and downloaded at HYPERLINK ''http://www.jhsph.edu/dept/IH/IIP/list'' www.jhsph.edu/dept/IH/IIP/list. More information about CHERG can be found at HYPERLINK ''http://www.cherg.org'' www.cherg.org.

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