



OPERATIONS MANUAL

FINAL DRAFT

JANUARY 20, 2009

HARVARD UNIVERSITY

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**INSTITUTE FOR HEALTH METRICS AND EVALUATION AT THE
UNIVERSITY OF WASHINGTON**

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JOHNS HOPKINS UNIVERSITY

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UNIVERSITY OF QUEENSLAND

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WORLD HEALTH ORGANIZATION

TABLE OF CONTENTS

- Chapter 1:** Introduction
- Chapter 2:** Participating Institutions
- Chapter 3:** Products and Deliverables
- Chapter 4:** Management Structure, Flow Diagrams, and Timeline
- Chapter 5:** Roles and Responsibilities
- Chapter 6:** Core Team Members
- Chapter 7:** External Advisory Board Members
- Chapter 8:** Analysis and Presentation of Regions
- Chapter 9:** Age Groups
- Chapter 10:** Mortality Envelopes (All-Cause Mortality)
- Chapter 11:** Causes of Death
- Chapter 12:** Concepts and Definitions for Quantifying Burden of Diseases, Injuries, and Risk Factors
- Chapter 13:** The GBD Study Cause Lists: Diseases and Injuries, Risk Factors, and Diseases as Risks
- Chapter 14:** Sequelae Definitions and Selection Criteria
- Chapter 15:** Disability Weights
- Chapter 16:** Years Lived with Disability (YLD) Estimation for Diseases and Injuries
- Chapter 17:** Using DisMod to Estimate Missing Epidemiological Parameters and Check Internal Consistency
- Chapter 18:** Comparative Risk Assessment and Diseases as Risk Factors
- Chapter 19:** Systematic Review
- Chapter 20:** Dealing with Bias and Missing Data
- Chapter 21:** Describing and Analyzing Uncertainty
- Chapter 22:** Publication Peer Review Process and Principles

CHAPTER 1

INTRODUCTION

OVERVIEW

The new Global Burden of Diseases, Injuries, and Risk Factors Study (the GBD 2005 Study), which commenced in the spring of 2007, is led by a consortium including Harvard University, the Institute for Health Metrics and Evaluation at the University of Washington, Johns Hopkins University, the University of Queensland, and the World Health Organization (WHO). It is the first major effort since the GBD 1990 Study to carry out a complete systematic assessment of the data on all diseases and injuries, and produce comprehensive and comparable estimates of the burden of diseases, injuries and risk factors for two time periods, 1990 and 2005. By November 2010 the project will produce a final set of estimates.

The GBD 2005 Study brings together a community of experts and leaders in epidemiology and other areas of public health research from around the world to measure current levels and recent trends in all major diseases, injuries, and risk factors, and to produce new and comprehensive sets of estimates and easy-to-use tools for research and teaching. This ambitious effort will be conducted systematically and transparently; both its methods and results will be made available to the public.

BACKGROUND

The original Global Burden of Disease Study (GBD 1990 Study) was commissioned by the World Bank in 1991 to provide a comprehensive assessment of the burden of 107 diseases and injuries and ten selected risk factors for the world and eight major regions in 1990 (1). The methods of the GBD 1990 Study created a common metric to estimate the health loss associated with morbidity and mortality. It generated widely published findings and comparable information on disease and injury incidence and prevalence for all world regions. It also stimulated numerous national studies of burden of disease. These results have been used by governments and non-governmental agencies to inform priorities for research, development, policies and funding.

The principle guiding the burden of disease approach is that the best estimates of incidence, prevalence, and mortality can be generated by carefully analyzing all available sources of information in a country or region, and correcting for bias. The disability-adjusted life year (DALY), a time-based measure that combined years of life lost due to premature mortality and years of life lost due to time lived in health states less than ideal health, was developed to assess the burden of disease. The GBD 1990 Study represented a major step in quantifying global and regional effects of diseases, injuries, and risk factors on population health.

In 2000, the World Health Organization began publishing regular GBD updates for the world and 14 regions (2). These revisions were aided by methodological improvements and more

extensive data collection that covered key aspects of the GBD, including mortality estimation, cause of death analysis, and measurement and valuation of functional health status. Standardized concepts and approaches to comparative risk assessment were applied to over 25 risk factors. New estimates for 2001 were published as part of the second revision of the Disease Control Priorities Project (3). In addition to these continuing efforts for better epidemiological quantification, the philosophical underpinnings for quantifying population health have been extensively explored as part of the overall effort to foster summary measures of population health.

OBJECTIVES

Despite the considerable efforts made and the methodological improvements achieved, important opportunities remain to greatly advance the quantification of the burden of diseases, injuries and risk factors.

First, there has not been a complete systematic assessment of the data on all diseases and injuries since the GBD 1990 Study. Such an assessment is particularly relevant because new sources of primary data have become available including vital statistics data, Demographic and Health Surveys, Multiple Indicator Cluster Surveys, World Health Surveys, and several national health interview and examination surveys. Second, new methods for estimating adult mortality, analyzing verbal autopsy data, modeling cause of death composition, computing attributable fractions for multiple risk factors, correcting for differential item functioning in health surveys, and imposing internal consistency constraints can be brought to bear. Third, better population-based methods and data are available to develop improved disability weights for the health states included in the GBD 2005 Study. Finally, there is a large community of epidemiologists and public health specialists who are familiar with the burden of disease concepts and methods in many countries and regions, and can contribute to methodological and empirical improvements.

The GBD 2005 Study has two major objectives. First, it will produce estimates of the burden of diseases, injuries and risk factors for 1990 and 2005, using new data and improved techniques. It will be collaborative at all levels, with coordination by a team of public health researchers from a number of leading research institutions and engagement of experts across study regions. The estimates, now organized in 21 regions covering the globe, will be comprehensive and consistent.

Second, the GBD 2005 Study will develop a series of tools for use by specific audiences, to standardize and broaden the burden of disease research and analysis. Revised computational tools will allow researchers around the world to apply the GBD burden of disease and comparative risk assessment techniques in a systematic way. Tailored publications will help policymakers and non-research audiences to interpret GBD concepts and utilize study results.

APPROACH

The GBD Study will focus on more than 220 diseases and injuries and more than 43 risk factors for 21 regions of the world. The GBD Study will not only serve to systematically incorporate the evidence on each major disease and risk factor into a coherent set of epidemiological estimates. It will also provide an opportunity for concerted work on new age- and sex-specific mortality estimates, disability weight measurement, estimates of probabilities of disabling sequelae, standardization of tools and methods for resolving inconsistencies, dealing with missing data and quantifying uncertainty. The GBD Study will conduct epidemiological reviews of all diseases, injuries, and risk factors; estimate mortality and causes of death for all countries in the world; derive new disability weights for an updated list of disabling sequelae, all leading to final, consistent and comprehensive estimates of the burden of diseases, injuries and risk factors for 1990 and 2005.

ORGANIZATION

A Core Team of scientists and methodologists will coordinate the GBD 2005 Study and ensure its steady progress along a 45-month time frame. The Core Team reunites the authors of the GBD 1990 Study and engages new leaders in the global health field to design and coordinate the research.

An invitation for participation in the GBD 2005 Study was announced in the summer of 2007, and more than 800 experts' applications were received. The experts were organized into approximately 45 scientific Expert Groups for specific diseases, injuries, and risk factors. These groups will conduct systematic reviews of the incidence and prevalence of diseases and disabling sequelae, and of exposure to and effects of risk factors. They will communicate their figures at defined intervals to the other Expert Groups and the Core Team in order to ensure consistency across conditions.

Responding to critiques and improvements in the field, the new GBD Study will make major progress in disability assessment, using new survey instruments to update disability weights and collect data on health states. Consistency checks and peer reviews will occur throughout the GBD 2005 Study to ensure that estimates of mortality, burden of disease, injuries and risk factors are systematically and cautiously generated. As an important quality check, the GBD 2005 Study embeds feedback and discourse among participants into its design.

BENEFITS

The GBD Study will provide four key benefits as a source of accurate knowledge and a vital tool for informed decision-making. First, the GBD 2005 Study separates epidemiological assessment from advocacy, creating evidence-based pictures of health patterns that can subsequently motivate responsible policy formulation and research. Major infectious diseases such as HIV, TB, and malaria have absorbed a great deal of attention, while “new” conditions, such as hearing loss and migraine, have only recently been included in the public

health agenda. The new GBD Study will use standard measures to ensure that all conditions receive systematic and objective analyses.

Second, the GBD 2005 Study combines information on disease and risk factor causes of premature mortality, morbidity, and disability to present a balanced assessment of health problems. The GBD 1990 Study brought visibility and legitimacy to conditions like depression and paralysis, which cause great suffering with little associated mortality, as well as conditions like road traffic injuries, which were formerly outside the scope of mainstream public health. The GBD 2005 Study has the potential to change common perceptions of global health.

Third, the GBD 2005 Study assesses the magnitude of health problems using standard units of measurement, such as disability-adjusted life years (DALYs). This study feature allows for lives in every part of the world to be valued equally, and creates a common unit of currency for making decisions about the costs and benefits of various health interventions.

Fourth, the GBD 2005 Study will focus from the outset on education and transparency, incorporating features such as an interactive website where experts can post information and actively discuss the GBD 2005 Study. Broadening the global community's engagement with population health metrics is a priority.

Improving the health and well-being of the world's population is a moral imperative and is essential for global stability and progress. The vast energies, technologies, and resources that are pouring into global health have given us the capacity to fight disease, remedy disability, and address the deep inequalities in health between populations. The new round of the Global Burden of Diseases, Injuries, and Risk Factors Study will provide the tools and knowledge to inform efforts for making truly effective interventions possible.

REFERENCES

- (1) Murray CJL, Lopez AD, eds. *The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020*. Cambridge, Harvard University Press on behalf of the World Health Organization and the World Bank, 1996.
- (2) World Health Organization. *The world health report 2000. Health systems: improving performance*. Geneva, World Health Organization, 2000. URL: http://www.who.int/whr/2000/en/whr00_en.pdf
- (3) Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL, eds. *Global burden of disease and risk factors*. New York, Oxford University Press and the World Bank, 2006.

CHAPTER 2

PARTICIPATING INSTITUTIONS

The following institutions are significantly involved in the Global Burden of Diseases, Injuries, and Risk Factors Study.

HARVARD UNIVERSITY

The Harvard University component is primarily based at the Harvard Initiative for Global Health (HIGH), involving faculty and graduate students from the Harvard School of Public Health.

HIGH is an interdisciplinary faculty initiative, with the founding goal to support and expand global health education, training, and research across Harvard University. It supports a number of large research projects and includes faculty and researchers from diverse disciplinary backgrounds.

The key investigators on this project have extensive experience relevant to the GBD 2005 Study including aspects of the design and implementation of the World Health Surveys and the Comparative Risk Assessment Study. These projects have all involved collaboration with experts and institutions across a wide range of countries, many of which in the developing world.

INSTITUTE FOR HEALTH METRICS AND EVALUATION AT THE UNIVERSITY OF WASHINGTON

The team at the University of Washington includes the GBD project's Principal Investigator and faculty members and staff from the Institute for Health Metrics and Evaluation. The Institute is associated with both the School of Medicine and the School of Public Health and Community Medicine. The University of Washington has a long history of research and service projects worldwide.

The mission of the Institute for Health Metrics and Evaluation is to monitor global health conditions and health systems, as well as to evaluate interventions, initiatives, and reforms. The Institute will provide high-quality and timely information on health so that policymakers, researchers, donors, practitioners, local decision-makers, and other health professionals can better allocate limited resources to achieve optimal results in improving population health.

Faculty and researchers, aided by a central management team, will guide the work of the Institute. Together, they will design and implement research, education, and evaluation projects which are relevant to the current needs and emerging challenges in global health. To

develop the cadre of young researchers crucial for sustaining the efforts in each area of its work, the Institute supports a post-bachelor and a post-doctoral fellows program.

JOHNS HOPKINS UNIVERSITY

The Department of International Health at the Johns Hopkins Bloomberg School of Public Health is committed to understanding the health problems of people in developing countries and underserved areas of the United States. As the oldest and largest department of international health in the world, it is uniquely equipped to develop affordable ways of protecting and improving health through health services and behavioral changes.

The key investigators on this project have extensive experience in developing, implementing, and managing programs and research on global health challenges; serving on international reference groups related to child survival and HIV/AIDS; and working in a range of developing countries. Collectively, the project team at Johns Hopkins offers expertise in epidemiology, infectious disease control and program evaluation, with rich experience in country collaboration and capacity building.

THE UNIVERSITY OF QUEENSLAND

The University of Queensland has established itself as one of the region's leading centers for public health research and teaching. Its School of Population Health aims to improve population health in Australia and throughout the world by researching the key and emerging issues in public health, forging strategic partnerships, and preparing the public health leaders of tomorrow through the pursuit of academic excellence.

Programs at the School cover international health, public health, health studies (including addiction studies and clinical epidemiology), nutrition, indigenous health, tropical health, biostatistics, and population health and health promotion.

The School has created a center of excellence in burden of disease research - The Center for Burden of Disease and Cost-Effectiveness. This center hosts research on both Australian and global burden studies and is in the unique position to lead high-quality burden and cost-effectiveness projects, while at the same time offering training on all aspects of the burden of disease methodology.

WORLD HEALTH ORGANIZATION

The World Health Organization, the United Nations' specialized agency for health, was established in 1948. WHO's objective, as set out in its Constitution, is the attainment by all peoples of the highest possible level of health. Health is defined in WHO's Constitution as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."⁽¹⁾

WHO is governed by 193 Member States through the World Health Assembly. The Assembly is composed of representatives from WHO's Member States. The main tasks of the World Health Assembly are to approve the Organization's program and budget for the following biennium and to decide on major policy questions. WHO's Secretariat comprises several thousand health professionals, other experts and support staff working at the headquarters in Geneva, and in the regions. There are six regional offices and more than 100 country offices. The latter are well-equipped to facilitate country work through their close links with the respective governments and extensive network of partners.

WHO's role in public health is not only to focus on setting global norms and standards, but also to contribute significantly to innovation in health, particularly through multi-country studies. WHO has an important comparative advantage over any health research organization in the world: it is able to combine standardized research in multi-country studies with its capacity to draw upon the prime intellectual resources anywhere in the world, and then translate research findings into public health policy priorities.

WHO's work for the Global Burden of Disease Study will take place in the Evidence and Information for Health Policy (EIP) cluster. The Department of Measurement and Health Information Systems (MHI) aims to provide information on epidemiology and the burden of disease. It produces the World Health Statistics and holds the central databases on health statistics and causes of death as reported by countries. It is also responsible for development of estimates of cause-specific mortality, incidence and prevalence of diseases, injuries and disability, and summary measures of population health.

REFERENCES

- (1) Constitution of the World Health Organization. *Basic Documents*, Forty-fifth edition, Supplement, October 2006. Geneva, World Health Organization, 2006:1. URL: http://www.who.int/governance/eb/who_constitution_en.pdf

CHAPTER 3

PRODUCTS AND DELIVERABLES

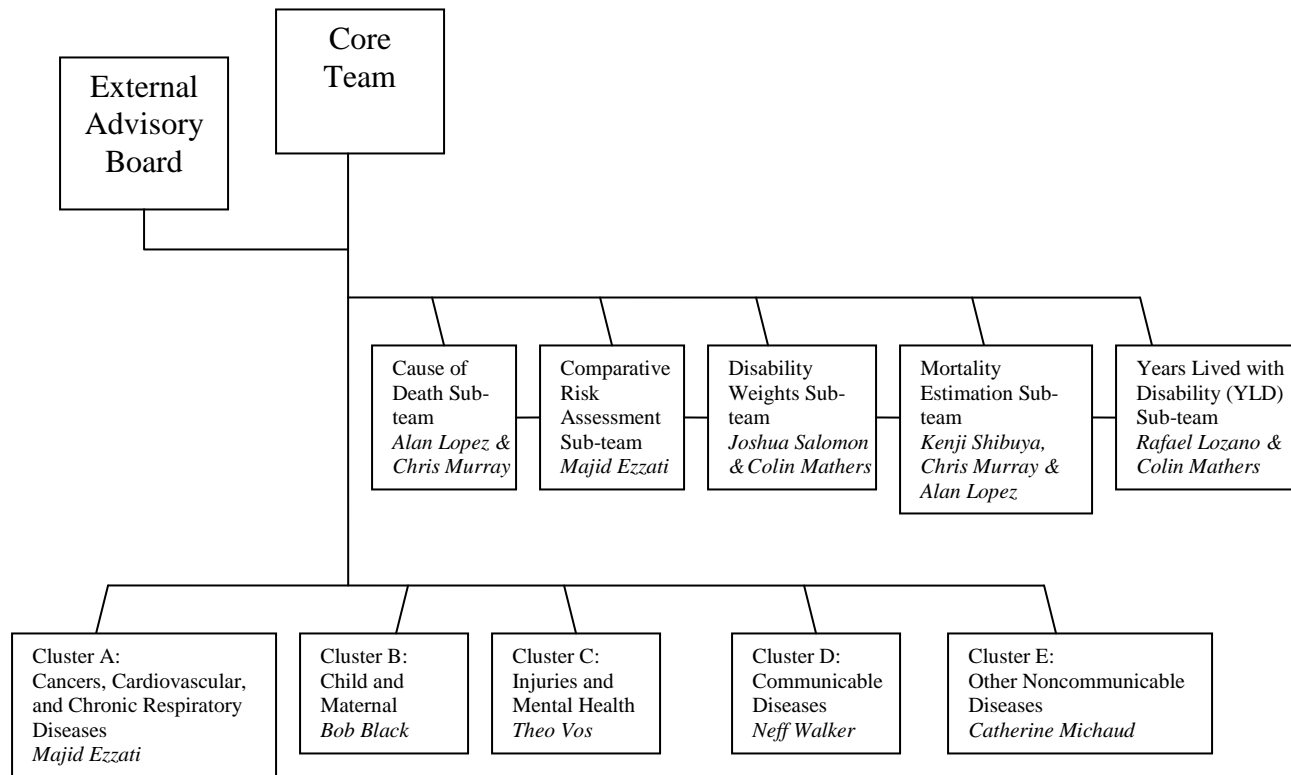
The set of ultimate products and deliverables of the Global Burden of Diseases, Injuries, and Risk Factors Study includes:

- Comprehensive estimates of the burden of diseases and injuries, by age, sex and region, for 1990 and 2005. Estimates should include deaths, years of life lost (YLL), and years lived with disability (YLD), incidence, prevalence and duration of cases and disabling sequelae.
- Comprehensive estimates of mortality and burden of disease attributable to selected risk factors by sex, age, and region for 1990 and 2005.
- Analysis of trends between 1990 and 2005 for all diseases, injuries, and risk factors.
- Software tools designed specifically to aid in the computation of disease and injury burden and comparative risk assessment, on a national and global level.
- Training curriculum and accompanying educational tools for policymakers, practitioners, and researchers interested in burden of disease and comparative risk assessment.

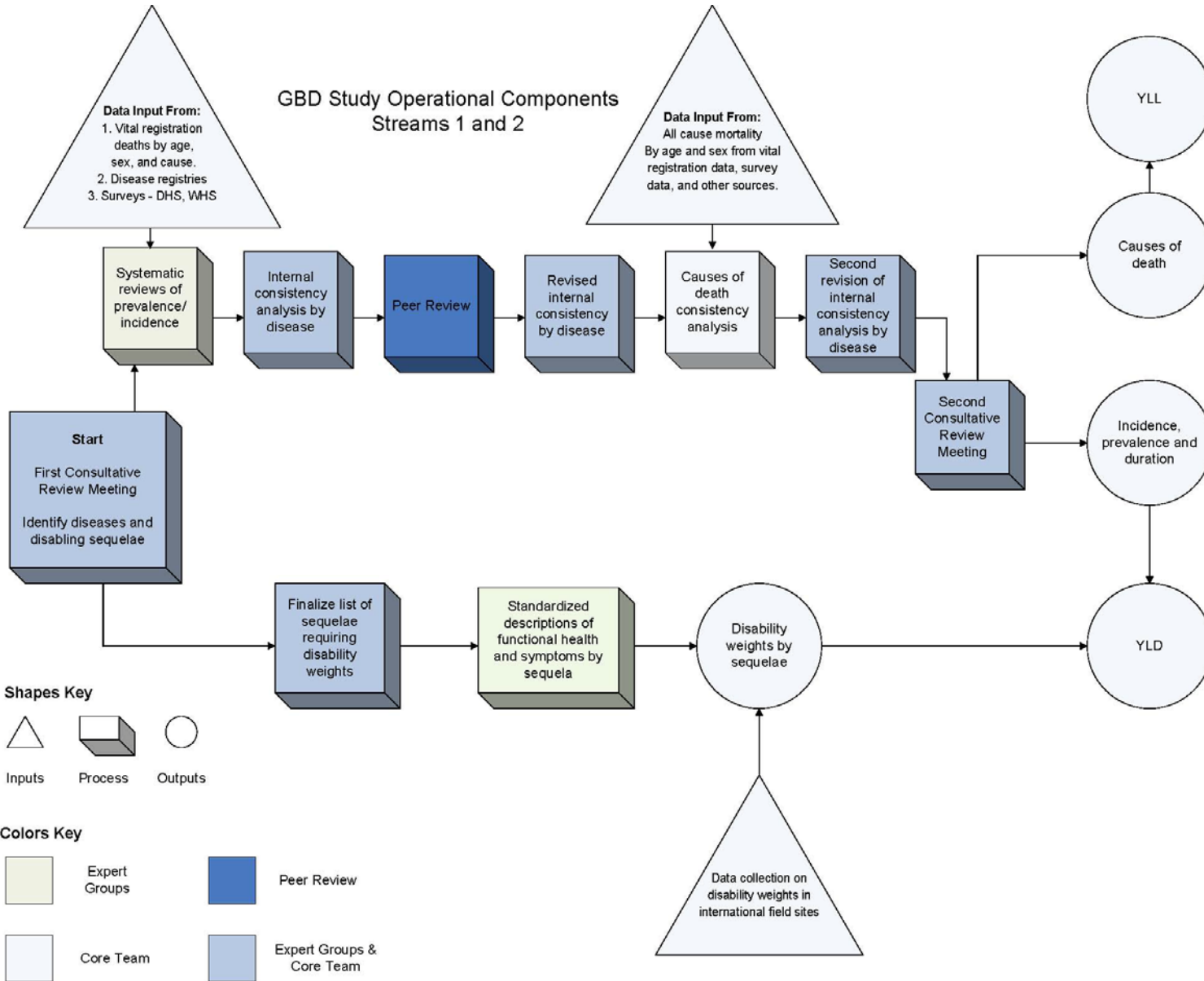
CHAPTER 4

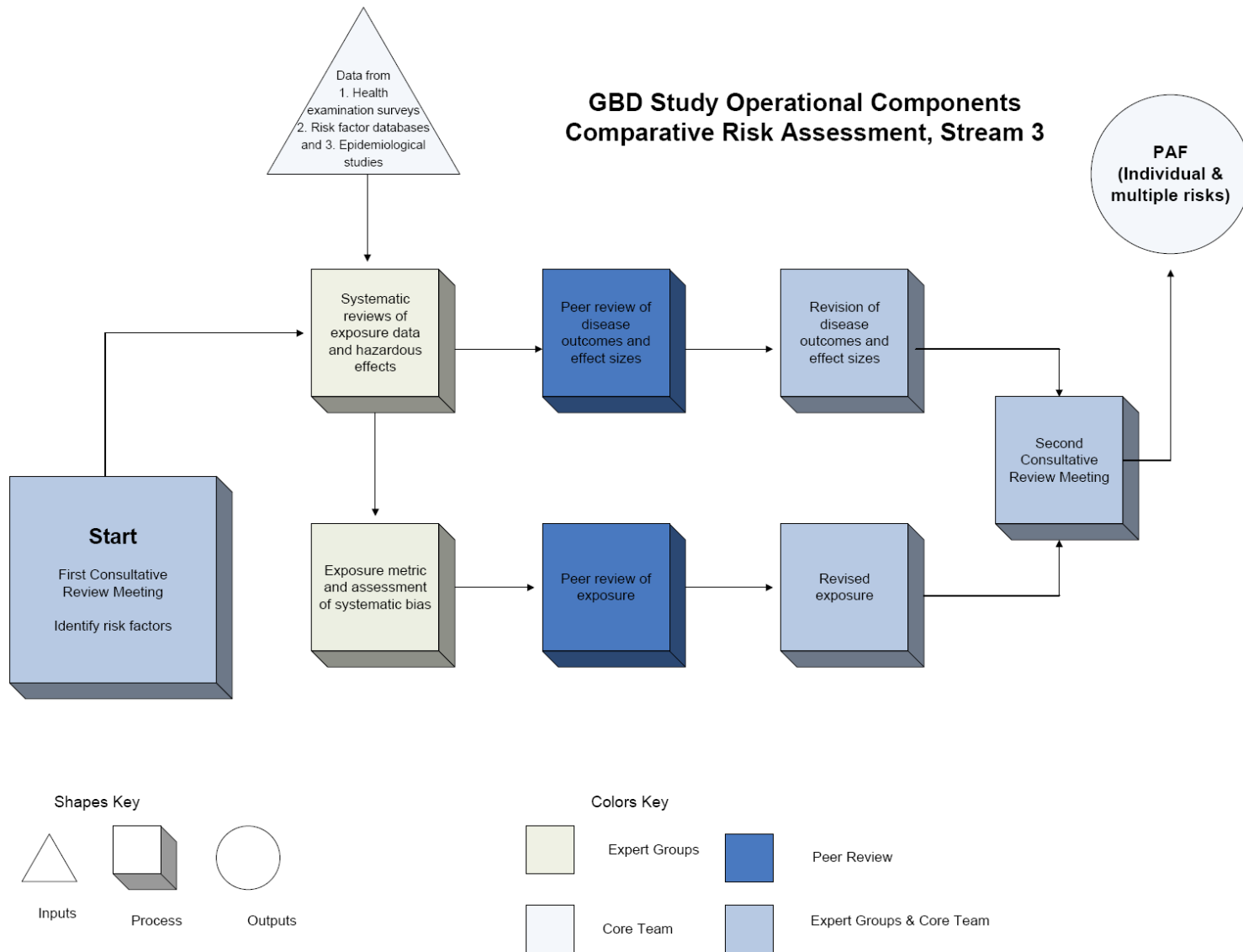
MANAGEMENT STRUCTURE, FLOW DIAGRAMS, AND TIMELINE

GBD STUDY ORGANIZATIONAL STRUCTURE



GBD Study Operational Components Streams 1 and 2





The GBD 2005 Study began on March 6, 2007, following an Executive Management Planning Meeting involving members of the Core Team. The GBD Study will coordinate the efforts of an international group of researchers and experts in order to produce comprehensive and comparable estimates of the global burden of diseases, injuries and risk factors for two time periods, 1990 and 2005. By November 2010 the GBD 2005 Study will produce a final set of estimates.

The GBD Study is divided into seven major activities with milestones that span the length of the project. Each major activity has been carefully planned to correspond to the work in other activities so that each area progresses at a similar pace. The activities are:

1. Disease, Injury, and Risk Factor Epidemiological Review
2. Mortality Estimation
3. Cause of Death Estimation
4. Disability Weights Measurement
5. Comparative Risk Assessment
6. Years Lived with Disability (YLD) Estimation
7. Tools and Curricula Development and Dissemination of Results and Products

The Disease, Injury, and Risk Factor Epidemiological Review will be managed by five Cluster Leaders, each facilitating a systematic review process undertaken by the Expert Groups. Sub-teams will also dedicate time and effort to Mortality Estimation, Cause of Death Estimation, Disability Weights Measurement, Comparative Risk Assessment, Years Lived with Disability (YLD) Estimation. The Core Team will manage the GBD 2005 Study estimates harmonization. The implementation of the project will be monitored by members of the Core Team and facilitated by a staff management team.

PHASE 1: MARCH 6, 2007 – DECEMBER 30, 2008

The first phase of the GBD 2005 Study will focus on establishing the Expert Groups, beginning the systematic epidemiological reviews, undertaking the central tracking of common data sources, and coordinating within Clusters to complete the first round of systematic epidemiological reviews. The process of recruiting experts started with the public announcement of the project in *The Lancet*, followed by a campaign to invite collaborators through international networks of disease associations and researchers previously involved with the burden of disease undertaking. The GBD Study's First Consultative Meeting occurred in September 2007; the External Advisory Board members, Core Team and a cross-section of participating experts attended. Experts will continue to join the project as it progresses, with the core assembled by the end of 2007.

During the first phase, the GBD 2005 Study will accomplish the following milestones:

- Finalize the list of diseases, injuries, risks and disabling sequelae, and establish the case definitions or health state descriptions for each.

- Recruit a cadre of disease experts to begin the systematic review of published and available unpublished studies, surveys, and other data sources to estimate incidence, prevalence, case fatality, and mortality from each disease, and injury and prevalence and incidence from each disabling sequelae.
- Conclude the first round of systematic reviews of incidence, prevalence, case fatality, and mortality for each disease and injury (for presentation in collaborators meetings in early 2009). Systematic reviews will yield estimates by age, sex, and country, and take initial steps towards regional estimates. For epidemiological parameters that can only be estimated from internal consistency analysis, in other words for which there are no direct measurements, these can be deferred until the step of regional internal consistency analysis. Some expert groups may choose to begin undertaking this themselves or at least develop and analytical plan for internal consistency work.
- Develop and finalize the standardized protocols for new data collection and analysis for estimation of disability weights.
- Establish the definition of risk factor exposure, the variable used to measure exposure in a population for each risk, and evidence on systematic bias in exposure and effect size data sources.
- Conclude the first round of systematic reviews of epidemiological studies, health surveys, health examination surveys, and other data sources to estimate risk factor exposure and effect sizes for presentation in collaborator meetings in early 2009.
- The Expert Groups will identify important comorbidities.
- The Core Team will then develop and provide standardization.
- Create prototype versions of improved DisMod, CodMod, and CRA software tools.
- Preliminary all-cause and cause-specific mortality estimates will be generated for each age, sex and GBD Study region.
- Host a training session on GBD methods for Core Team members and interested participating experts.
- Phase 1 Cluster Meetings to report on progress and facilitate coordination.

PHASE 2: JANUARY 1, 2009 - DECEMBER 31, 2009

The second phase of the GBD 2005 Study will focus on coordination between the Clusters and the Core Team to check the first round of epidemiological reviews for consistency, send them for peer review, and revise based on internal and external reviews. The Core Team will continue meeting on a regular basis to ensure the steady progress of the work of reviewing and revising the first round of estimates.

During the second phase, the GBD 2005 Study will accomplish the following milestones:

- Organize and hold review meetings in January and February, 2009 for epidemiological reviews and estimates produced by expert groups with Core Team and a representative from each Expert Group

- Region-specific age-sex cause of death estimates based on cause of death data sources will be discussed and provided to Expert Groups at the January and February meetings.
- Expert Group representatives who attended meeting to work with rest of their respective Expert Group to revise estimates and look for more data based on the peer-feedback from the review meeting.
- Internal consistency, requiring DISMOD, to be completed by Core Team in consultation with Expert Groups (or by Expert Groups if they so choose).
- Core Team to dialogue with Expert Groups via e-mail and send complete sets of internally consistent estimates for External Peer Review.
- External Peer Review completed and Expert Groups revise estimates, completing the second round of systematic reviews of incidence, prevalence, case fatality, and mortality for each disease and injury, and for risk factor exposure and effect sizes.
- Expert Groups will conclude the revised round of systematic reviews of epidemiological studies, health surveys, health examination surveys, and other data sources to estimate risk factor exposure.
- Undertake data collection for estimation of disability weights.
- Write instruction manuals for DisMod and CodMod software tools.
- Phase 2 Cluster Meetings to report on progress and facilitate coordination.

PHASE 3: JANUARY 1, 2010 - NOVEMBER 30, 2010

During the third phase of the GBD 2005 Study, the estimates will be finalized for publication. The Second Consultative Meeting will be held to facilitate coordination and the finalization of estimates. Additionally, all computational tools with instruction manuals, and the research- tailored curriculum will be finalized.

During the third phase, the GBD 2005 Study will accomplish the following milestones:

- Produce final internally consistent epidemiological assessments of incidence, prevalence, mortality, and disabling sequelae.
- Produce final child mortality, adult mortality, and all cause mortality estimates that are analyzed for trends and arranged into league tables with data citations.
- Compute disability weights and calculate YLD.
- Produce final estimates of age- and sex-specific exposure to risk factors for each of the designated regions, population attributable fractions, and estimates of risk attributable to mortality and disability with analysis of trends.
- Finalize league tables for YLL, Causes of Death, and YLD for 1990 and 2005 and for each of the designated regions, and analyze trends.
- Complete the production of new National Burden of Disease computational tools.
- Second Consultative Meeting to facilitate coordination and finalize estimates.
- Publicly release Global Burden of Diseases, Injuries and Risk Factors Study estimates.

CHAPTER 5

ROLES AND RESPONSIBILITIES

The GBD Study involves hundreds of individuals from around the world. To facilitate coordination and enhance collaboration, several specific groups have complementary responsibilities.

EXTERNAL ADVISORY BOARD

The External Advisory Board will serve as a primary liaison to key stakeholders in research and policy networks for global health. It will advise the Core Team on a variety of strategic matters. The Board's principal goal will be to broaden the global impact of the burden of disease work. Toward that end, it will assist in securing outlets for publication and presentation of findings, and will advise on ways of sharing these with the public, NGOs, policymakers, and the research community as part of a broader dissemination strategy. Finally, the External Advisory Board will also function as a sounding board for the Core Team, raising questions and giving feedback on the issues of study design, inclusion of participants, and fundraising.

GBD CORE TEAM

The Core Team consists of a group of scientists from Harvard University, the Institute for Health Metrics and Evaluation at the University of Washington, Johns Hopkins University, the University of Queensland, and the World Health Organization.

The primary role of the Core Team is to coordinate the overall project, technically as well as logistically. The institutional leader of the project will be the Institute for Health Metrics and Evaluation at the University of Washington, where the project's core management will be based. The Core Team will:

- Ensure consistency of the study approach across the different Expert Groups.
- Support the Expert Groups in their work by providing templates; answering questions about estimation techniques and approaches; providing guidance on epidemiological reviews; conducting burden estimation and comparative risk assessment training for interested participants; and ensuring that data resources are shared across the project.
- Define age groups and regions into which the final estimates will be disaggregated.

- Finalize a set of diseases, injuries, and risk factors for which estimates will be produced based upon the collective input of the Expert Groups.
- Collect and assess centralized data sources for overall mortality by age and region.
- Establish mortality envelopes by assessing total child and adult mortality for all countries by age and sex.
- Collect and assess centralized data sources for causes of death (e.g. national vital registration data, disease registries, major health surveys) together with the epidemiological information collated by the Expert Groups that can be used for cause of death estimation.
- Finalize a list of disabling sequelae based upon the collective input of the Expert Groups and formalize definitions for them that are consistent regardless of the underlying disease cause of the sequelae.
- Establish envelopes for selected impairments including vision loss, hearing loss, mental retardation and consult with relevant expert groups to ensure consistency of estimates for related disabling sequelae for specific causes.
- Estimate the prevalence by age, sex and region of key impairments that are disabling sequelae of more than one disease including cognitive impairment, anaemia, visual impairment and hearing loss.
- Carry out data collection to inform the estimation of disability weights for disabling sequelae using standardized protocols.
- Perform a set of analytic consistency checks of submitted data and preliminary estimates across age, region, sex, and condition.
- Organize peer review of the epidemiological evidence and preliminary estimates produced by the Expert Groups.
- Create and maintain an archive of data sources used in the epidemiological reviews. The archive will include a bibliographic list of sources, and where possible - the actual datasets or source articles themselves.
- Create tools for use in estimation and analysis. Prior to being distributed to a wider audience, the tools will be shared with participants and improved as a result of their feedback.
- Finalize coherent and consistent estimates of the burden of diseases, injuries, and risk factors. Publish this set of estimates as the ultimate end-product of the GBD 2005 Study on behalf of the project participants. The final estimates will include total mortality, years of life lost, and years lived with disability caused by diseases and injuries, disaggregated by sex, age, and region. In addition, the final estimates will comprise mortality and burden of disease attributable to major risks disaggregated by sex, age, and region.

CLUSTER LEADER

The Expert Groups are organized into five Clusters for management purposes. Note that the five Clusters are not intended to be substantively significant divisions of the overall

GBD; they have been selected for managerial effectiveness across the collaborating institutions. Each Cluster has a Cluster Leader who is a member of the Core Team. It is expected that some Expert Groups will work with others outside of their own Cluster. The Cluster leaders can facilitate this process. Cluster Leaders will:

- Provide a direct link back to the Core Team for any questions, concerns or requests from the Expert Groups.
- Help to direct questions about burden of disease estimation and comparative risk assessment techniques and approaches to the right members of the Core Team.
- Work with the Expert Groups to address the challenges encountered during the epidemiological reviews.
- Facilitate communication and coordination among the groups, i.e. regularly contacting the Expert Groups' Leaders to summarize progress to date, report findings, and ensure that different groups dealing with similar challenges are communicating effectively.
- Provide initial feedback on the consistency of the produced results.
- Provide analytical support when needed.

EXPERT GROUPS

The Expert Groups are organized to be loosely coincident with condition-specific or risk-factor-specific interests. Each group will have an Expert Group Leader or Co-Leaders, Core Members, and Corresponding Members. Each Expert Group will agree upon and submit its own estimates and epidemiological reviews to the Core Team, and will:

- Draft precise definitions of each disease, injury, and risk factor in consultation with the Cluster Leader and the Core Team.
- Draft precise definitions of sequelae mapped to conditions in consultation with the Core Team, especially to ensure that sequelae definitions are consistent across the project.
- Where groups are working on diseases and injuries, undertake systematic reviews of both published and unpublished literature and studies to amass data on incidence and duration, or on other inputs like prevalence, remission, and case fatality that allow estimating incidence and duration.
- Where groups are working on risk factors, undertake a systematic review of all published and available unpublished epidemiological studies, health surveys, and health examination surveys. This includes both randomized and observation studies, as well as biological evidence to establish the disease and injury outcomes associated with each risk factor and other data sources that can be used to estimate risk factor exposure. This will also be used to establish the magnitude of their hazardous effects for these diseases and injuries.
- Create an explicit audit trail of all sources and data used. This work will be aided by templates provided by the Core Team which can be adapted to fit the needs of individual groups.

- Conduct all reviews according to the guidelines provided in the present manual to ensure that the Expert Groups are consistent in their approach.
- Revise the epidemiological reviews and estimates taking into consideration the feedback from the Core Team and the peer review process. The basic parameters are that all epidemiological reviews must cover data from 1990 to 2005, and be age-, region-, and sex- specific whenever possible.

EXPERT GROUP LEADER

Each Expert Group will have a designated Leader or Co-Leaders whose primary responsibility is to facilitate the work of the group as a whole. The Expert Group Leader is responsible for achieving consensus on the estimates and data that are presented to the Core Team. He/she must be the focal point for any funding proposals submitted by the Expert Group to the Core Team. The Expert Group Leaders will contact the Cluster Leaders most frequently in order to draw attention to questions as they arise, facilitate the communication among members, and ensure that the GBD 2005 Study deadlines are met.

EXPERT GROUP CORE MEMBER

Each Expert Group will have several Core Members. They will meet on a regular basis, occasionally in person but more frequently by phone and e-mail, to review progress to date and formulate strategies for pursuing the work further. They will carry out the epidemiological reviews most directly and undertake the key elements of the Expert Group's responsibilities outlined above.

EXPERT GROUP CORRESPONDING MEMBER

Each Expert Group will have numerous Corresponding Members. These individuals will not participate in the regular meetings, but will receive the materials and latest data from the Expert Group on a periodic basis. They will be given an opportunity to review these materials and data, and to provide input on the work. On occasion, they may be asked to add to specific components or give advice on particular elements of the GBD 2005 Study.

CROSS-CUTTING ISSUES CORE MEMBER

These individuals have either expertise that reaches across the clusters, experience and insights from their past and current work which can be valuable to the project, or other characteristics and interests such that their participation in a broader-focused group is ideal. Cross-Cutting Issues Core Members will be coordinated by a member of the Core Team and asked for their input, advice and feedback at critical junctures of the GBD 2005 Study.

CROSS-CUTTING ISSUES CORRESPONDING MEMBER

These individuals may be periodically called on to review the ongoing work of the Core Members of the Cross-Cutting Issues Expert Group. Occasionally they may be asked to add to specific components or offer their advice on a discrete element of the GBD 2005 Study. The Expert Group Leader or a member of the Core Team may contact them with progress reports or to share the ongoing research.

CHAPTER 6

CORE TEAM MEMBERS

Robert Black
Professor and Chair, Department of International Health
Johns Hopkins Bloomberg School of Public Health

Ties Boerma
Director, Department of Measurement and Health Information Systems
World Health Organization

Majid Ezzati
Associate Professor of International Health
Harvard School of Public Health
Harvard Initiative for Global Health

Dean Jamison
Professor
Institute for Health Metrics and Evaluation
University of Washington

Alan D. Lopez
Professor and Head of School
School of Population Health, University of Queensland

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*Chairman of the Core Team and Principal Investigator

CHAPTER 7

EXTERNAL ADVISORY BOARD MEMBERS

A key component of the GBD 2005 Study's integrated approach is an External Advisory Board which is comprised of members from major global health organizations. The External Advisory Board will serve as a primary liaison to the main stakeholders in research and policy networks for global health. The Board's principal aim will be to broaden the global impact of the burden of disease work.

The members of the External Advisory Board are:

Tim Evans
World Health Organization

Roger Glass
Fogarty International Center

Jeff Koplan
Emory University

Richard Peto
University of Oxford

Osman Sankoh
INDEPTH Network

Sally Stansfield
Health Metrics Network

Richard Suzman (liaison to the project)
National Institute for Aging

Michael Wolfson
Statistics Canada

Gonghuan Yang
Chinese Academy of Medical Sciences

CHAPTER 8

ANALYSIS AND PRESENTATION OF REGIONS

The GBD 1990 Study presented estimates of total mortality, years of life lost, and years lived with disability due to diseases and injuries for eight regions of the world. A later innovation allowed for estimates of mortality and disability attributable to major risks for these same eight regions. This iteration of the study will present estimates in 21 distinct geographic regions.

The objectives of regionalization are twofold: first, to define regions that are as epidemiologically homogeneous as possible, so that information from detailed studies in one country can plausibly be extrapolated to other countries in the region; and second, related to the first, to create burden estimates that are useful to individual countries in planning for health sector activities. The regions were chosen using mortality estimates from the World Health Organization and the United Nations, in addition to current knowledge on country-specific epidemiological conditions. The process of defining regions was based on the following principles:

1. All regions are based on broad geographic regions or continents.
2. All regions are comprised of no fewer than two countries.
3. Countries are grouped based on child and adult mortality levels and major causes of death in each country.
4. Despite the fact that income is clearly related to epidemiologic profiles, neither income nor national population had an impact on the end result of regionalization.

Each region was systematically named based on a consistent naming convention as follows: [Geographic region], [Modifier].

The 21 GBD regions are as follows:

ASIA PACIFIC, HIGH INCOME

~

Brunei Darussalam
Japan
Republic of Korea
Singapore

ASIA, CENTRAL

~

Armenia
Azerbaijan
Georgia
Kazakhstan
Kyrgyzstan
Mongolia
Tajikistan
Turkmenistan
Uzbekistan

ASIA, EAST

~

China
Democratic People's Republic of Korea
Hong Kong
Macao
Taiwan

ASIA, SOUTH

~

Afghanistan
Bangladesh
Bhutan
India
Nepal
Pakistan

ASIA, SOUTHEAST

~

Cambodia
Christmas Island
Cocos Islands
Indonesia
Lao People's Democratic Republic
Malaysia
Maldives
Mauritius
Myanmar
Philippines
Reunion

Seychelles
Sri Lanka
Thailand
Timore Leste
Viet Nam

AUSTRALASIA

~

Australia
New Zealand

CARIBBEAN

~

Anguilla
Antigua and Barbuda
Aruba
Bahamas
Barbados
Belize
Bermuda
British Virgin Islands
Cayman Islands
Cuba
Dominica
Dominican Republic
French Guiana
Grenada
Guadeloupe
Guyana
Haiti
Jamaica
Martinique
Montserrat
Netherlands Antilles
Puerto Rico
Saint Barthelemy
Saint Kitts and Nevis
Saint Lucia
Saint Martin
Saint Vincent and the Grenadines
Suriname
Trinidad and Tobago
Turks and Caicos Islands

US Virgin Islands

EUROPE, CENTRAL

~

Albania
Bosnia and Herzegovina
Bulgaria
Croatia
Czech Republic
Hungary
Montenegro
Poland
Romania
Serbia
Slovakia
Slovenia
The Former Yugoslav Republic of Macedonia

EUROPE, EASTERN

~

Belarus
Estonia
Latvia
Lithuania
Republic of Moldova
Russian Federation
Ukraine

EUROPE, WESTERN

~

Akrotiri and Dhekelia
Aland Islands
Andorra
Austria
Belgium
Channel Islands
Cyprus
Denmark
Faeroe Islands
Finland
France
Germany

Gibraltar
Greece
Greenland
Guernsey
Holy See
Iceland
Ireland
Isle of Man
Israel
Italy
Jersey
Liechtenstein
Luxembourg
Malta
Monaco
Netherlands
Norway
Portugal
San Marino
Spain
Svalbard
Sweden
Switzerland
United Kingdom

LATIN AMERICA, ANDEAN

~

Bolivia
Ecuador
Peru

LATIN AMERICA, CENTRAL

~

Colombia
Costa Rica
El Salvador
Guatemala
Honduras
Mexico
Nicaragua
Panama
Venezuela

LATIN AMERICA, SOUTHERN

~

Argentina
Chile
Falkland Islands (Malvinas)
Uruguay

LATIN AMERICA, TROPICAL

~

Brazil
Paraguay

NORTH AFRICA / MIDDLE EAST

~

Algeria
Bahrain
Egypt
Iran (Islamic Republic of)
Iraq
Jordan
Kuwait
Lebanon
Libyan Arab Jamahiriya
Morocco
Occupied Palestinian Territory
Oman
Qatar
Saudi Arabia
Syrian Arab Republic
Tunisia
Turkey
United Arab Emirates
Western Sahara
Yemen

NORTH AMERICA, HIGH INCOME

~

Canada
United States of America
Saint Pierre et Miquelon

OCEANIA

~

American Samoa
Cook Islands
Fiji
French Polynesia
Guam
Kiribati
Marshall Islands
Micronesia (Federated States of)
Nauru
New Caledonia
Niue
Norfolk Island
Northern Mariana Islands
Palau
Papua New Guinea
Pitcairn
Samoa
Solomon Islands
Tokelau
Tonga
Tuvalu
Vanuatu
Wallis and Futuna Islands

SUB-SAHARAN AFRICA, CENTRAL

~

Angola
Central African Republic
Congo
Democratic Republic of the Congo
Equatorial Guinea
Gabon

SUB-SAHARAN AFRICA, EAST

~

Burundi
Comoros
Djibouti
Eritrea
Ethiopia
Kenya
Madagascar
Malawi

Mayotte
Mozambique
Rwanda
Somalia
Sudan
Uganda
United Republic of Tanzania
Zambia

SUB-SAHARAN AFRICA, SOUTHERN

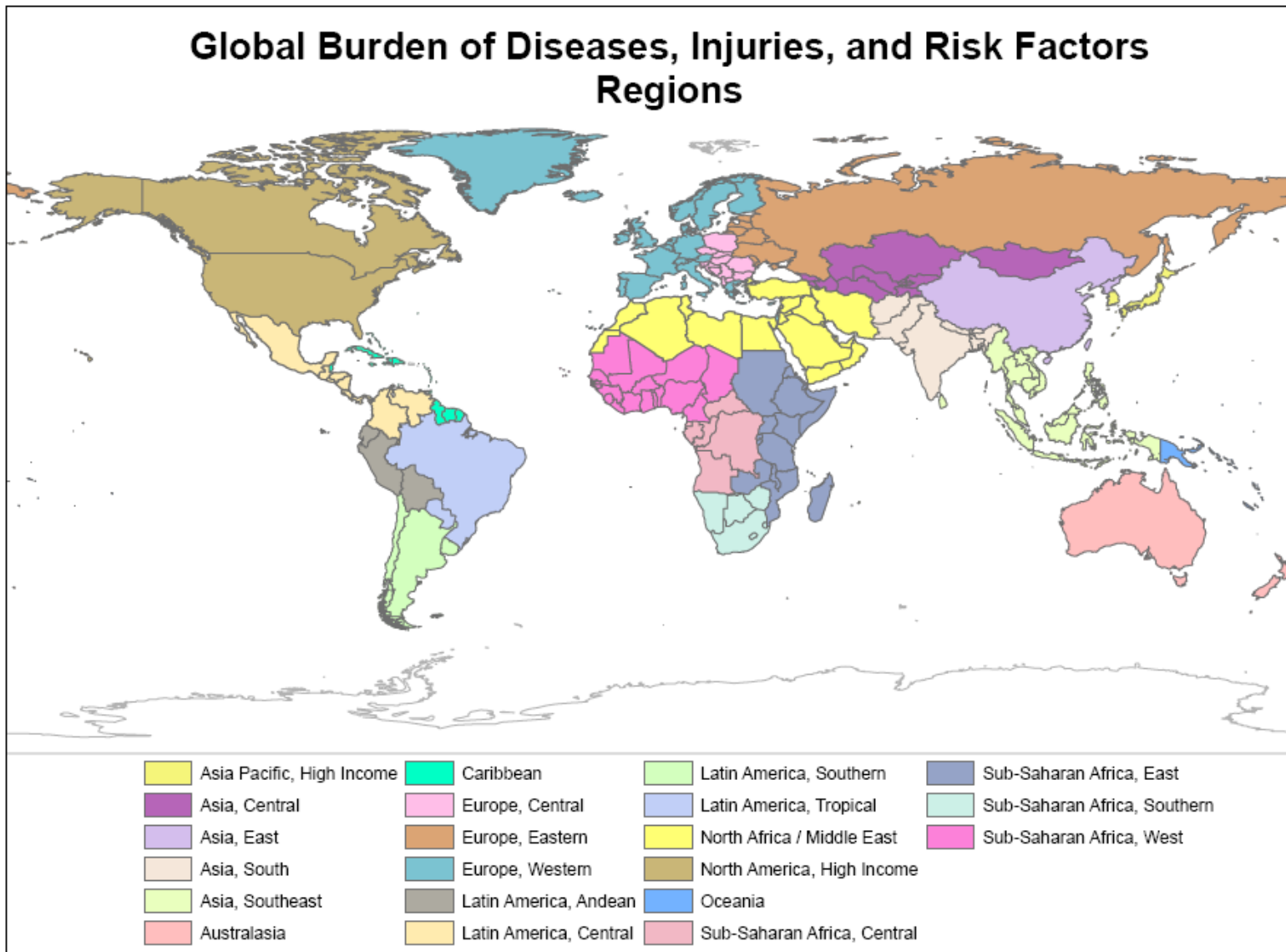
~

Botswana
Lesotho
Namibia
South Africa
Swaziland
Zimbabwe

SUB-SAHARAN AFRICA, WEST

~

Benin
Burkina Faso
Cameroon
Cape Verde
Chad
Cote d'Ivoire
Gambia
Ghana
Guinea
Guinea-Bissau
Liberia
Mali
Mauritania
Niger
Nigeria
Saint Helena
Sao Tome and Principe
Senegal
Sierra Leone
Togo



CHAPTER 9

AGE GROUPS

AGE

The age groups used in the compilation of epidemiological parameters and burden estimates are slightly different from those used for the compilation of mortality and cause of death data. The expanded list of deaths by cause is anticipated to be of more relevance to assessments of selected risk factors than burden of disease.

AGE GROUPS FOR BURDEN OF DISEASE CALCULATIONS

<1 month
1 – 11 months
1 – 4 years
5 – 9 years
10 – 14 years
15 – 19 years
20 – 24 years
25 – 34 years
35 – 44 years
45 – 54 years
55 – 64 years
65 – 74 years
75 – 84 years
85+ years

AGE GROUPS FOR MORTALITY AND CAUSE OF DEATH COMPILATION

Antepartum stillbirths (28 weeks or later, but before start of labor)

Intrapartum stillbirths (after the start of labor)

Early neonatal (completed days of life 0 to 6)

Late neonatal (completed days of life 7 to 27)

28 days – 5 completed months

6 – 11 months

1 – 4 years

5 – 9 years

10 – 14 years

15 – 19 years

20 – 24 years

25 – 29 years

30 – 34 years

35 – 39 years

40 – 44 years

45 – 49 years

50 – 54 years

55 – 59 years

60 – 64 years

65 – 69 years

70 – 74 years

75 – 79 years

80 – 84 years

85+ years

SEX

Deaths by cause and burden calculations will all be made separately by sex (with the possible exception of antepartum stillbirths, for which information by sex may be limited).

- Male
- Female

CHAPTER 10

MORTALITY ENVELOPES (ALL-CAUSE MORTALITY)

A key component in burden of disease analysis, with a particular emphasis on consistency and comparability, is provided by all-cause mortality “envelopes.” These envelopes consist of numbers of all-cause deaths and are constructed from information that allows the estimation of mortality by age and sex independent of cause. Competing claims for the magnitude of deaths from various causes assigned following the ICD concept of underlying cause (see Chapter 11) must be reconciled within this envelope: i.e. the sum of deaths from all specific causes for any age-sex group must sum to the total number of deaths for that age-sex group estimated via the data sources and methods described below. From the estimated age-specific mortality rates, life tables for the populations of the GBD 2005 Study regions can be derived using standard methods.

Comparable estimates of mortality envelopes will be developed by the Core Team for all countries with populations estimated to be 250,000 or more in 2005 (countries with populations of less than 250,000 will in general be treated in regional aggregates), and for smaller countries with non-problematic sources of data. The estimates will be developed for the period from 1990 to 2005, by sex and for:

- five-year age groups from age 5 to age 84;
- an open age interval 85+;
- stillbirths;
- deaths in the early neonatal, late neonatal, one to five months, six to 11 months, 12 to 59 months.

Deaths will then be cumulated across countries within each GBD Study region and by GBD Study age groups.

The Core Team will also develop and provide the Expert Groups with population estimates by region in order to ensure that consistent numbers are used.

Methods of estimating mortality vary widely around the world, according to data sources and assessments of quality. In general, deaths under and over age 5 are treated differently. Efforts to systematically evaluate the available sources of data to measure child mortality for all countries from 1970 to 2005 have already been completed for the GBD 2005 Study and published in *The Lancet* (1). This analysis will be revised using similar methods and any new vital registration, survey or census data that become available during the Study.

Adult mortality estimation is more challenging. Data sources and empirical relationships that can be used to estimate adult mortality include: civil registration systems; results from censuses or surveys on deaths in a household in a recent time period; results from

surveys or censuses on the survival of parents or siblings; the observed relationship between child and adult mortality in countries with good data systems. The Mortality Estimation Sub-team will apply an array of demographic methods to the available data sources to estimate adult mortality. These methods include application of a wide range of death distribution techniques to estimate completeness of civil registration methods. Part of the research of a group of investigators involved in the GBD 2005 Study but funded by the Bill & Melinda Gates Foundation Grand Challenges in Global Health is to develop improved methods for assessing the completeness of vital registration data. These new methods will be incorporated into the ongoing efforts to estimate adult mortality by country for 1990 and 2005 for the GBD 2005 Study. Novel methods are also being developed to analyze the available sibling survival data. For some countries, there will be no data based on which to estimate adult mortality directly. In these cases, the observed relationship between levels of adult and child mortality and the way this relationship varies as a function of certain key covariates will be used to generate adult mortality estimates with wide uncertainty intervals.

REFERENCES

- (1) Murray CJL, Laakso T, Shibuya K, Hill K, Lopez AD. Can we achieve Millennium Development Goal 4? New analysis of country trends and forecasts of under-5 mortality to 2015. *The Lancet*, 2007 Sep 22, 370(9592):1040-1054.

EXPERT GROUP RESPONSIBILITY

The development of mortality envelopes for the 21 regions will be undertaken by the Core Team. It may be useful for the Expert Groups to become familiar with how this work is done.

CHAPTER 11

CAUSES OF DEATH

Following the approach of the International Classification of Diseases (ICD) of assigning each death to a single underlying cause, the Cause of Death Sub-team will produce a preliminary set of age-, sex- and cause-specific mortality estimates for each region that sum to all-cause mortality. This “categorical” approach to causal attribution of mortality (see Chapter 12 for more discussion) has been the long-standing tradition in health statistics. In reality, many deaths are multicausal and to reflect the more complex causal pathways that lead to death, the GBD 2005 Study will also analyze the number of deaths that would be averted if a cause were eliminated. This is often referred to as counterfactual estimates of mortality by cause. In this section, we outline the approach to generating preliminary and final estimates of mortality according to the ICD principle of a single underlying cause of death. Counterfactual estimates of deaths caused by different diseases are discussed in Chapter 12.

Cause of death information for estimating the disease burden comes from many sources. These sources vary in terms of three dimensions: first, the extent and quality of the information about the events leading up to an individual’s death; second, the knowledge, training and experience of the individual assigning underlying, immediate and associated causes of death; and third, the method used to assign a unique ICD code to the certified death. In most high-income countries, extensive information from medical records is available for most deaths; the death certificate is completed by a physician and a standardized computer algorithm is used to assign the ICD code. At the other end of the spectrum, information is only available through an interview of the household members of the decedent; a cause is assigned by a health worker and ICD coding is completed by the same or another health worker. Finally, for the majority of deaths no information is recorded. The challenge in cause of death assessment is to use information from many different data sources of varying depth and quality in order to generate comparable estimates of mortality by cause.

In practice, we can identify five sources of cause of death data:

VITAL REGISTRATION SYSTEMS WITH MEDICAL CERTIFICATION

Some of the problems with this type of data include variable completeness of registration and the associated issue that some causes of death may be more likely to be captured than others; low quality of certification and coding, and extensive use of ill-defined or garbage codes as causes of death. For cause of death analysis certain ICD codes are considered garbage codes and are distributed using empirical algorithms. Table 1 at the end of this chapter lists these redistributable garbage codes.

VERBAL AUTOPSY WITH PHYSICIAN CERTIFICATION AND CODING

A number of demographic surveillance sites, a limited number of national surveys and some national sample registration systems have collected data from household members on the signs and symptoms prior to death. These data have then been used by physicians to assign a cause of death. So far, this information has had limited use in informing national and the global burden of disease due to problems of comparability. New efforts both on standardizing instruments for verbal autopsy and for assigning causes of death hold out hope that these data may be more useful for the GBD 2005 Study (1).

DEATHS IN HOSPITAL WHERE A CAUSE OF DEATH HAS BEEN CERTIFIED

While deaths in hospital are not a random or representative sample of deaths in the community, recent methodological work has indicated that the selection bias for dying in a hospital can be corrected (2). Deaths in hospital where these deaths are certified and coded according to the ICD may prove to be a useful adjunct to other data sources on causes of death.

DISEASE/INJURY REGISTRIES

For some diseases such as cancers, population registries have been set up to capture all incident cases. Where these registries are well operated with a high rate of follow-up to the household, they can be used to assess case-fatality rates and even age-specific death rates. However, many registries have poor follow-up and tend to under-estimate mortality.

EPIDEMIOLOGICAL RESEARCH STUDIES

For some diseases, there are cohort studies which provide information on case-fatality and mortality rates for a specific sample that is often not representative but chosen for convenience. If used carefully, these can potentially inform estimates of mortality by cause.

For the GBD 2005 Study, the Cause of Death Sub-team will apply a variety of methods to address the data problems arising from systemic issues. The latter include a high proportion of ill-defined or “garbage” codes, which need to be reallocated to specific diagnoses; incomparability of cause of death assignment across various datasets; uncertain diagnostic procedures for determining cause of death from verbal autopsy reports; and biases in inferring community cause of death patterns from hospital data. Methods and procedures to resolve some of these challenges have already been developed, and others will be made available during the course of the GBD 2005 Study.

Additional methodological research led by several members of the Expert Group as part of the Gates Grand Challenges Project in Population Health Metrics will also inform the cause of death analyses for the GBD 2005 Study.

Many of the disease/injury Expert Groups will have access to detailed epidemiological studies for populations, and/or disease registries or official records from other sources that will contain useful condition-specific cause of death data, or information from which causes of death can be estimated, at least for some region/age/sex groups. The Expert Groups are encouraged to identify all such sources, however fragmentary; to evaluate them carefully for representativeness; to share them when appropriate; and to use them when preparing their condition-specific estimates of epidemiological parameters.

Simultaneously, the Core Team will be actively searching for all available vital registration data and other centrally available datasets on causes of death such as demographic surveillance sites data, sample registration data, and verbal autopsy studies. As a first step, and to serve as a guide to the Expert Groups in developing their epidemiological estimates, the Core Team will prepare the first round estimates of mortality by cause for all diseases and injuries in the GBD list, by age, sex and region. The Core Team will carefully evaluate national and international sources of mortality data for quality and completeness. It will adjust the data where necessary for incompleteness and misdiagnosis, using the methods previously applied in the GBD 2005 Study or new methods where available, as described above.

After several iterations within the Core Team, a plausible set of first round detailed cause-specific estimates will be developed that match the envelopes of deaths by age and sex estimated for each region using standard demographic techniques. The preliminary cause of death estimates will be an intermediate research product of the GBD 2005 Study. They will be made available to all the Expert Groups and the public. The Expert Groups will carefully review these estimates and suggest changes, based on their work to achieve internally consistent disease estimates of mortality and other epidemiological parameters for their respective diseases/injuries. The Core Team will use input from Expert Groups and work closely with them in order to produce the best estimates of cause-specific mortality for the diseases/injuries in question. Experience has shown that claims on the number of deaths assigned according to the underlying cause principles of the ICD summed across diseases may in some regions exceed the number of deaths estimated from all causes. Resolving these inconsistencies across diseases may take several iterations in view of the need to preserve consistency with other epidemiological parameters. It will be the Core Team's responsibility to resolve these inconsistencies in a clear and transparent fashion for all study participants.

As with all estimation efforts for the GBD 2005 Study, the Expert Groups will systematically and comprehensively document all data sources used, data quality evaluations, and the detailed methods employed to obtain cause of death estimates at each stage of the process. When inconsistencies between the preliminary cause of death

estimates and those produced by the Expert Groups are evaluated, careful documentation of the Expert Groups' work will be essential.

Finally, the set of cause-specific estimates developed via this collaboration will have to be assessed by the other Expert Groups. The Second Consultative Meeting towards the end of the GBD 2005 Study will provide an opportunity for an extensive review across the different groups. Their comments will then be incorporated into the final revision of the cause of death figures. This revision is envisioned as a collaborative process involving the Expert Groups and the Core Team, but the main responsibility for resolving inconsistencies will rest with the Core Team.

TABLE 1 REDISTRIBUTABLE GARBAGE CODES FOR CAUSE OF DEATH ANALYSIS

REFERENCES

- (1) Murray CJ, Lopez AD, Feehan DM, Peter ST, Yang G. Validation of the symptom pattern method for analyzing verbal autopsy data. *PLoS Medicine*, 2007 Nov 20, 4(11):e327.
- (2) Murray CJ, Lopez AD, Barofsky JT, Bryson-Cahn C, Lozano R. Estimating population cause-specific mortality fractions from in-hospital mortality: validation of a new method. *PLoS Medicine*, 2007 Nov 20, 4(11):e326.

CHAPTER 12

CONCEPTS AND DEFINITIONS FOR QUANTIFYING BURDEN OF DISEASES, INJURIES, AND RISK FACTORS

INTRODUCTION

The disability-adjusted life year (DALY) is a standardized metric that can be used to quantify loss of healthy years of life due to dying prematurely or to living with the health consequences of diseases, injuries or risk factors. What is meant by “lost healthy years of life” in the context of burden of disease analysis, and how can this notion be related to diseases, injuries or risk factors, and to disability? This chapter provides an overview of the framework that connects these concepts and their measurement. The chapter aims to clarify the tasks of enumerating lists of causes and sequelae.

There are two broad approaches to measurement of non fatal outcomes in health statistics. The first is based on the presence or absence of diseases and injuries. The second is based on the assessment of functional health status (that is, levels of functioning in a set of health domains such as mobility, cognition, vision, hearing, etc). One of the objectives of the GBD 2005 Study is to unify these approaches by:

- conceptualizing the loss of health as decrements in functioning in one or more health domains;
- quantifying the “average loss of health” for disease or injury “sequelae” as years lived with disability (YLD), and thus causally attributing losses of health to diseases, injuries, and their risk factors using empirical epidemiological evidence; and
- making measurement of non-fatal outcomes commensurate with mortality outcomes through a common time-based approach that counts lost years of healthy life.

In addition to the strategy for measuring health loss, there are two traditions in causal attribution of death or loss of health to diseases, injuries, and risk factors: *categorical attribution* and *counterfactual analysis* (1). In *categorical attribution*, an event such as death is attributed to a single cause (e.g. a disease, injury or risk factor) or a group of causes according to a defined set of rules such as the International Classification of Diseases (ICD) system (2). In *counterfactual analysis*, the contribution of one or a group of causes to death or loss of health is estimated by comparing the observed levels of health in a population to the levels of health that would be expected under some alternative hypothetical scenario (referred to as the counterfactual), including the absence of or reduction in the disease(s) or risk factor(s) of interest.

The disease and injury cause list provides the primary analytic framework for the calculation of YLL, YLD and DALYs in the GBD 2005 Study. Deaths and non-fatal health states are *categorically* attributed to diseases and injuries in this mutually exclusive list which is in principle comprehensive and complete. Functional health status outcomes are mapped into disease cases and sequelae for the estimation of YLD. The mortality and burden of disease attributable to risk factors are estimated using *counterfactual* methods.

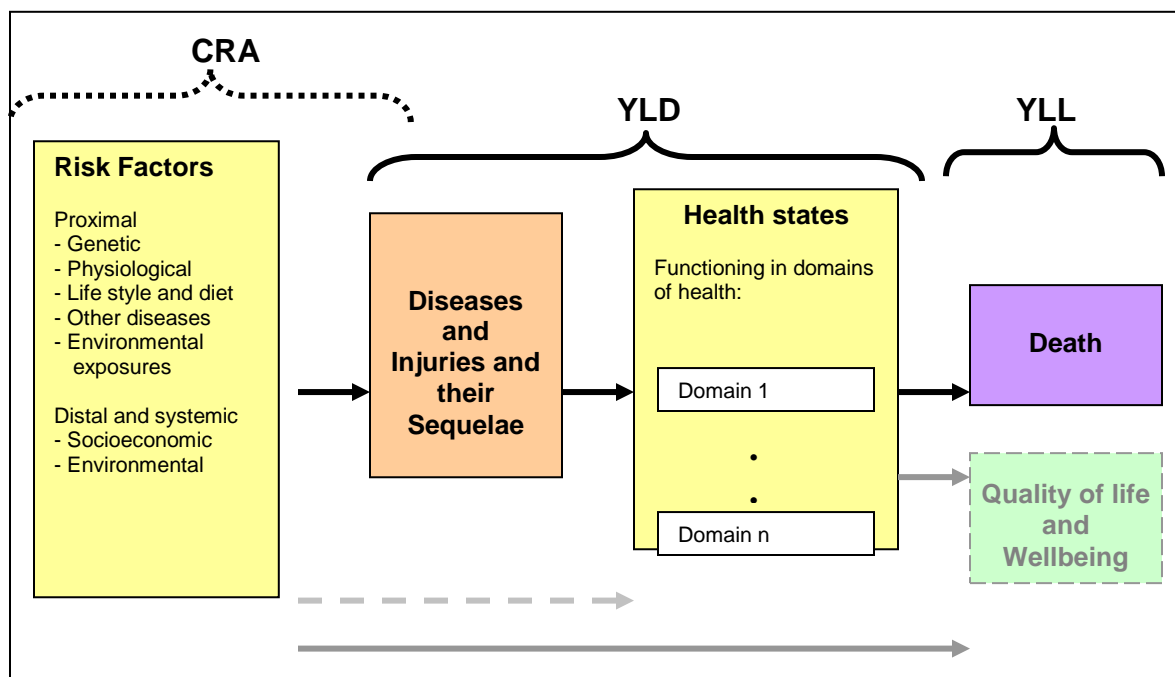
A clear understanding of the GBD 2005 Study’s conceptualization of risks, diseases, injuries, sequelae and health states is important for ensuring the consistency and validity of the approaches used by the Expert Groups in estimating epidemiological parameters and disability weights for the calculation of YLD.

CONCEPTUAL FRAMEWORK

Figure 1 provides a simplified conceptual schema for quantifying the loss of healthy life due to diseases, injuries and risk factors. The health state of a person is defined in terms of functioning within a set of “health domains” at a moment in time. The scope and definition of these domains is discussed in detail below, but we note here that such domains would include impairments in body functions and structures such as vision, hearing, and pain, and domains of more complex human operations such as mobility, cognition and communication.

Health states may be viewed as the consequences of diseases and injuries or their risk factors. In other words, diseases and injuries or their risk factors lead to a series of health experiences that may be understood in terms of transitions through different health states. Health states do not refer to general well-being (which is a broader construct) or to aspects of participating in society, although they clearly affect these other aspects of life and may be affected by them.

FIGURE 1 A SIMPLIFIED CONCEPTUAL FRAMEWORK FOR BURDEN OF DISEASE ANALYSIS



DISEASES AND DISORDERS

It is not always possible to define rigid boundaries between risk factors, diseases and disorders, and specific functional impairments. These boundaries are to some extent a matter of convention. The International Classification of Diseases (2) has not attempted to define diseases and disorders. However, working documents for the ICD-11 revision process have listed the following criteria:

Diseases (including disorders/conditions) are a set of dysfunctions in any of the body systems defined by:

1. Symptomatology - manifestations: known pattern of signs, symptoms and related findings
2. Etiology: an underlying explanatory mechanism
3. Course and outcome: a distinct pattern of development over time
4. Treatment response: a known pattern of response to interventions
5. Linkage to genetic factors: e.g. genotypes, patterns of gene expression
6. Linkage to interacting environmental factors

In general, diseases/disorders should not be defined in terms of distress, impairment, disability, or functioning per se, although definitions may include reference to specific symptoms, sequelae and disabling outcomes. In the GBD 2005 Study, an important additional property that may assist in deciding whether a cause should be seen as a disease/disorder rather than a risk factor is that:

7. Health states, sequelae, outcomes, and death can be categorically and causally attributed to the disease in persons without significant comorbid conditions.

For example, in a person with diabetes mellitus the typical stream of health states and occurrence of sequelae such as neuropathy or retinopathy can be attributed with reasonable certainty to the disease process. On the other hand, where an entity causally raises the risk of certain outcomes but categorical attribution at the individual level is not possible, the entity must be treated in a counterfactual approach and is likely better classified as the consequence of a risk exposure than as a disease. Thus, raised blood pressure is treated as a risk factor rather than a disease in the GBD 2005 Study because: (a) cardiovascular disease events cannot be categorically attributed to the raised blood pressure at the individual level and (b) raised blood pressure does not necessarily follow a distinct pattern of development over time with a known and predictable pattern of signs, symptoms and sequelae.

HEALTH STATES, DOMAINS, DISABILITY AND FUNCTIONING

Any quantification of functional health status must be based on a specified set of health domains. These domains include body functions such as breathing and digestion; senses

such as vision, hearing and pain; and more complex functions such as ambulation and cognition. Beyond these universally recognized domains of human health, widely used health status measurement instruments, such as SF-36, EQ-5D or the Health Utilities Index, include a number of dimensions that are so closely related to health that they provide convenient proxy information on functional health including self-care, the ability to carry out usual activities and instrumental activities of daily living. Some instruments also blur the line between health and well-being and seek to measure other elements of “quality of life” such as personal relationships and enjoyment of life. The GBD Study has adopted a core domains approach to defining and measuring functional health status, which focuses more narrowly on functional health domains to the exclusion of broader aspects of well-being.

The functional health status approach raises important issues related to the term “disability.” In the GBD 1990 Study’s formulation of the metric for health loss, the term disability was chosen to stress a vision of health that goes beyond the absence of disease and emphasizes decreases in functioning. The term has a number of different meanings to different groups. In particular it is not seen by some groups as a synonym or proxy for “loss of health.” However, the current GBD Study continues to use “disability” as a synonym or proxy for “loss of health” in the terminology for YLD and DALY, in view of the widespread use and recognition of these terms.

The definition of functioning may be understood in two different ways: in terms of *capacity* or *performance*. Performance refers to a person’s functioning in the current environment. Capacity refers to a person’s performance in a standard environment (e.g. a well-lit, non-slippery surface for assessing mobility). To the extent that performance reflects environmental barriers, which can vary with time, social or physical setting, and as individual circumstances change, it is probably not congruent with most notions of health. Thus, if a person cannot climb flights of stairs in his/her usual environment because the stairs are too steep, most people would not say that the person’s health state had changed if the stairs were modified to be less steep. This is consistent with the notion of health as an attribute of individuals rather than environments (though environmental factors may be causal for health states).

The GBD Study thus conceptualizes “loss of health” as decrements in capacity in health domains. A further requirement for computing YLD is that functioning on multiple domains be aggregated into an assessment of the overall decrement in health associated with a particular health state, which is referred to as a “disability weight.” The health state may be summarized as a vector of values quantifying functional capacity on each domain, while the disability weight represents an overall scalar quantification of the health level associated with the multidimensional state. The procedures for deriving disability weights are discussed in Chapter 15.

DISEASE AND INJURY CASES AND SEQUELAE

The GBD Study links loss of health to disease and injury causes through the concepts of cases and sequelae. For incident cases of a given disease or injury, there will be a distribution of current and future health states (as defined above), which reflect the experience of health until remission or death for each incident case. The GBD Study maps the distribution of health states for any disease or injury to a small set of discrete entities for which epidemiological estimates and YLD calculations are made. The GBD Study uses the term “sequela” as an umbrella term to describe this set of discrete entities. Thus the GBD 2005 Study’s “sequelae” may include only the disease case itself, or the disease case plus several clinical sequelae, or several disabling sequelae.

For a cause for which the disease case itself is the only sequela, the disability weight refers to the average overall health level that characterizes the entire distribution of health states experienced across individuals and by each individual over time until remission or death. Other diseases may have several distinct sequelae (in the clinical sense) which occur in a subgroup of cases, and these may be chosen as the GBD 2005 Study sequelae. For example, the GBD 2005 Study sequelae for diabetes mellitus include neuropathy, retinopathy, diabetic foot, and amputation. For other diseases, sequelae may be defined in terms of an array of health states characterized by different severity levels, rather than the traditional clinical definition of sequelae. For example, the GBD 2005 Study has two sequelae for glaucoma: low vision and blindness. Note that clinical glaucoma per se is not included as a GBD Study “sequela.”

For a given disease or injury cause, the choice and definition of cases and sequelae are based on the natural history of the disease, identification of the paths in that history associated with significant loss of functioning, and the availability of data to estimate prevalence and transition rates. Issues in the choice of sequelae are discussed in more detail in Chapter 14, together with some detailed examples.

For each disease or sequela, YLD is calculated from the estimated incidence, the average duration until remission or death (or transition to another sequela), and the average disability weight. Within this framework, an individual may have more than one disabling sequela at the same time. The disability weight for a disabling sequela refers to the average health loss for individuals with that condition in the absence of these comorbidities. Without adjustment for comorbidities, the implicit assumption is that multiple sequelae in the same person combine additively, which may not accurately describe the real effects of comorbidity on functional health. In this revision of the GBD, we will identify combinations of sequelae with significant prevalence, measure directly the combined health losses associated with these combinations in estimating disability weights (see Chapter 15), and adjust YLD estimates to reflect deviations from additive effects. In addition, following the practice in studies such as the Australian Burden of

Disease study, we will use empirically based algorithms for correcting for comorbidities that occur due to chance.

RISK FACTORS

Any entity that raises the probability of disease/injury incidence or death can be treated as a risk factor. Thus determinants of health such as poverty, dietary factors, diseases such as hepatitis B, and impairments such as blindness can all be treated as risk factors for loss of health. Their effects on deaths and DALYs from the complete list of disease and injury causes is quantified using a counterfactual analysis approach. The GBD Study will quantify deaths and disease burden attributable to a number of environmental, lifestyle, dietary, and physiological risk factors, and, to the extent possible, those of a number of genetic factors, and systemic environmental and socioeconomic factors.

The GBD Study will also consider a small subset of diseases as risk factors for other diseases and injuries, as described in Chapter 14. Figure 1 acknowledges this by showing the scope of the comparative risk assessment (CRA) analysis as extending partially over the disease/disorder/injury box.

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CHAPTER 13

THE GBD STUDY CAUSE LISTS: DISEASES AND INJURIES, RISK FACTORS, AND DISEASES AS RISKS

INTRODUCTION

The primary organizational framework for calculating the numbers of deaths, YLL, YLD, and DALYs is the disease and injury underlying cause list. Deaths and non-fatal health outcomes are categorically attributed to diseases and injuries in this list. In principle the list provides a series of mutually exclusive and collectively exhaustive categories. This chapter:

- summarizes the criteria for selection of the disease and injury categories for the GBD 2005 Study;
- defines these categories in terms of ICD-10 codes (ICD-9 codes are available if needed);
- outlines the process for review and revision of this cause list by the Expert Groups;
- describes the criteria used for selecting risk factors and diseases that are treated as risk factors for other diseases, whose attributable mortality and burden will be calculated using counterfactual methods (see Chapter 12);
- lists the selected risk factors and diseases as risks;
- describes the process for review and revision of these lists.

DISEASE AND INJURY CAUSE CATEGORIES

The GBD 1990 Study (*I*) classified disease and injury causes using a tree structure. The first level of disaggregation comprised three broad cause groups:

- Group I: Communicable, maternal, perinatal, and nutritional conditions
- Group II: Noncommunicable diseases
- Group III: Injuries

Group I causes consist of the cluster of conditions whose mortality typically declines at a faster pace than all-cause mortality during the epidemiological transition. In high-mortality populations, Group I dominates the causes of death, whereas in low-mortality populations, it accounts for only a small proportion of deaths.

Each Group is divided into major subcategories. For example, cardiovascular diseases and malignant neoplasms (cancers) are two major cause subcategories of Group II. Beyond this level, there are two further disaggregation levels. The major cause subcategories are closely based on the chapters of the International Classification of Diseases (ICD) (2), with a few significant differences. Whereas the ICD classifies chronic respiratory diseases and acute respiratory infections into one chapter, the GBD 2005 Study cause classification included acute respiratory infections in Group I. Similarly, infectious diseases such as meningitis and cystitis included in other ICD chapters– neurological conditions and genito-urinary conditions, respectively– have also been moved to Group I.

The disease and injury cause list for the GBD 2005 Study largely follows the GBD 1990 Study's principles. However it also takes into account the increased public health interest in estimates for pathogen-specific conditions. This interest is due to the policy implications for prevention and vaccination interventions and the increased availability of data on the etiological agents for diseases such as diarrhoea and acute lower respiratory infections. The general principles for revising the cause list are:

- Disease and injury cause categories that include a significant fraction of deaths or disease burden in at least one of the GBD 2005 Study regions according to provisional evaluation at the beginning of the GBD 2005 Study.
- Causes which may not have a high disease burden are included if they are important for public health policy or health services and expenditures (e.g. polio and appendicitis).
- Causes are not so broad as to be uninformative for public health policy (e.g. cardiovascular diseases as a single cause group) and not so specific as to make cross-national and cross-regional comparisons difficult due to the large number of categories and the likelihood of spurious patterns arising from differences in diagnostic practices.
- To the extent possible, cause categories are defined in terms of the 2-digit ICD-10 codes (many countries with death registration data do not report deaths by 3 digit code categories, and in every case where a cause category is defined in terms of 3 digit codes it will be necessary for the Cause of Death Sub-team or the relevant Expert Group to impute the numbers of deaths for the more detailed code lists).
- A cause category can be assigned as an underlying cause of death at the individual level using ICD-10 or GBD categorical assignment rules (thus, although distal causes such as tobacco smoking (Z72) do have ICD-10 codes, they are not assignable as underlying causes of death using ICD rules).
- Disease and injury cause categories are mutually exclusive (at the same level of the tree structure) and collectively exhaustive.

Deaths are categorically attributed to one underlying cause, primarily using ICD rules and conventions. Where ICD rules are ambiguous, the GBD 2005 Study may need to

develop supplementary rules. The ICD category “Symptoms, signs and ill-defined conditions” is not listed as one of the major causes in the GBD classification system. Deaths assigned to this category, as well as some other codes used for ill-defined conditions and so called garbage codes (see Chapter 11), are reassigned to specific causes of death in the GBD classification scheme. From the perspective of generating useful information to compare cause of death patterns, or to inform health policy making, this is important to allow non-biased comparisons of cause of death patterns across countries and regions.

A number of disease causes also act as factors that increase the risk of death from other diseases which have specific ICD codes. Examples include cancers caused by earlier infectious disease episodes (e.g. liver cancer due to hepatitis infection) and suicide caused by mental disorders (schizophrenia, depression, etc). Counterfactual analysis for the estimation of the total deaths attributable – versus directly assigned – to such diseases is discussed later in this chapter.

Table 1 lists the proposed GBD Study disease and injury cause categories with corresponding ICD-10 codes. Mappings of code lists for ICD-9 and earlier versions are available from the Core Team. Note that the ICD code list for a cause does not imply that the Expert Groups need to assess the epidemiology for every specific disease in the ICD code list, only for appropriate groupings of cases/sequelae with non-trivial disabling outcomes (as specified by the sequelae list in Chapter 14). Thus, for example, arterial stenosis not resulting in an infarction is included in the ICD list for cerebrovascular disease, but can safely be ignored for the YLD calculations.

In general, the list of sequelae associated with a given disease or injury cause will reflect the array of significant decrements in health along core domains of functioning that follow from a particular cause. There will be envelopes for impairments relating to vision, hearing, cognition, anaemia and possibly some others such as infertility (see Chapter 14). For some of these, there will need to be a residual category for the proportion of cases that are not unique sequelae of causes in the GBD 2005 Study list. Where residual impairment categories are included in Table 1 they are left unnumbered (in terms of the tree codes of the form II.A.1 which refers to the first disease, mouth cancer, in category A, malignant neoplasms, of Group II conditions), and they will probably not be displayed as a separate cause in output tables, but included in the residual categories.

In general, age at incidence or death is not a criterion for definition of cause groups. Rather, causes are defined epidemiologically only, and consistently across ages. Thus incident cases or deaths due to infections in the neonatal period would generally be included in the relevant infectious disease categories. There are however some causes which only arise in the perinatal period (such as prematurity, hydrops fetalis, Rh incompatibility) and these are grouped in a second-level category provisionally labeled “Perinatal and infant causes” in Group I. By definition, incident cases of these conditions

would only occur in the first month of life, although deaths may occur outside the neonatal period (e.g. a death at age 2 months due to prematurity).

The ICD-10 codes listed here are the codes corresponding to each cause category if the ICD-10 coding rules are correctly applied. For mortality analysis, there will also be ill-defined codes in some chapters which will need to be redistributed in the cause of death analyses carried out by the Cause of Death Sub-team. Such ill-defined codes are in most cases not shown in the table, and will not generally be relevant for the Expert Groups' work.

TABLE 1 GBD STUDY DISEASE AND INJURY CAUSE LIST¹

Table 1 GBD Study Disease and Injury Cause List 1 (January 2009)

N-GBD Code	O-GBD Code	Description	ICD10 Codes
I	G1	Communicable, maternal, perinatal and nutritional conditions	A00-A39 (except A28.9), A42-A63 (except A48.0, A48.3, A49.9), A65-B81, B83-B88 (except B83.9), B90-B92, B94.0, B94.1, B95.0, B95.1, B95.2, B95.3, B95.4, B95.5, B95.6, B95.7, B95.8, B97, D50-D53, D64.9, E00-E02, E40-E63, E64.0, E64.1, E64.2, E64.3, G00.0, G00.1, G00.2, G00.3, G00.8, G00.9, G03-G04, H65-H66, J00-J22, J85, N30, N34, N39.0, N70-N73, O00-P94, P96 (except P96.9)
IA	G2	Tuberculosis	A15-A19, B90, P37.0
IB	G3	HIV/AIDS	B20-B24
IC	G4	STDs excluding HIV	A50-A63, N70-N73
IC1	G5	Syphilis	A50-A53
IC2	G6	Chlamydia	A55-A56
IC3	G7	Gonorrhoea	A54
IC4	G8	Other STDs	A57-A63, N70-N73
ID	G9	Intestinal infectious diseases	A00-A09
ID1	G10	Diarrhoeal diseases	A00, A02-A04, A06-A09
ID1a	G11	Cholera	A00
ID1b	G12	Salmonella infections	A02
ID1c	G13	Shigellosis	A03
ID1d	G14	Enteropathogenic Escherichia coli infection	A04.0
ID1e	G15	Enterotoxigenic Escherichia coli infection	A04.1

GBD 2005 STUDY OPERATIONS MANUAL – FINAL JANUARY 2009

ID1f	G16	Campylobacter enteritis	A04.5
ID1g	G17	Amoebiasis	A06
IG1h	G18	Cryptosporidiosis	A07.2
ID1i	G19	Rotaviral infection	A08.0
ID1j	G20	Other diarrheal disease	A04 (except A04.0, A04.1, A04.5), A07-A09 (except A07.2, A08.0)
ID2	G21	Typhoid and paratyphoid fevers	A01
ID3	G22	Other intestinal infectious diseases	A05
IE	G23	Selected vaccine preventable childhood diseases	A33-A37, A80, B01, B05-B06, B26, B91, P35.0, P35.8
IE1	G24	Diphtheria	A36
IE2	G25	Whooping cough	A37
IE3	G26	Tetanus	A33-A35
IE4	G27	Poliomyelitis	A80, B91
IE5	G28	Varicella (chickenpox)	B01, P35.8
IE6	G29	Measles	B05
IE7	G30	Rubella	B06, P35.0
IE8	G31	Mumps	B26
IF	G32	Meningitis and encephalitis	A39, A83-A87, B94.1, G00.0, G00.1, G00.2, G00.3, G00.8, G00.9, G03-G04
IF1	G33	Meningitis	A39, A87, G00.0, G00.1, G00.2, G00.3, G00.8, G00.9, G03
IF1a	G34	Streptococcus pneumoniae meningitis	G00.1
IF1b	G35	Haemophilus influenzae type B (Hib) meningitis	G00.0
IF1c	G36	Neisseria meningitidis meningitis or meningococcaemia	A39
IF1d	G37	Other meningitis	A87, G00.2, G00.3, G00.8, G00.9, G03
IF2	G38	Encephalitis	A83-A86, B94.1, G04
IG	G39	Hepatitis	B15-B19, P35.3
IG1	G40	Hepatitis A	B15
IG2	G41	Hepatitis B	B16-B19 (except B17.1, B17.2, B18.2), P35.3
IG3	G42	Hepatitis C	B17.1, B18.2
IG4	G43	Hepatitis E	B17.2
IH	G44	Malaria	B50-B54, P37.3, P37.4
IH1	G44.1	Plasmodium falciparum malaria	B50
IH2	G44.2	Plasmodium vivax malaria	B51
IH3	G44.3	Mixed and others	B52-B54, P37.3, P37.4
li	G45	Parasitic and vector diseases	A71, A74.0, A82, A90-A91, A95, B55-B57, B65, B67-B74 (except B74.3, B74.4, B74.8, B74.9), B76-

GBD 2005 STUDY OPERATIONS MANUAL – FINAL JANUARY 2009

			B81, B94.0
Ii1	G46	Leishmaniasis	B55
Ii2	G47	African Trypanosomiasis	B56
Ii3	G48	Chagas disease	B57
Ii4	G49	Schistosomiasis	B65
Ii5	G50	Cysticercosis	B69
Ii6	G51	Echinococcosis	B67
Ii7	G52	Dracunculiasis	B72
Ii8	G53	Lymphatic filariasis	B74 (except B74.3, B74.4, B74.8, B74.9)
Ii9	G54	Onchocerciasis	B73
Ii10	G55	Trachoma	A71, A74.0, B94.0
Ii11	G56	Dengue	A90-A91
Ii12	G57	Yellow fever	A95
Ii13	G58	Rabies	A82
Ii14	G59	Intestinal nematode infections	B68, B70-B71, B76-B81
Ii14a	G60	Ascariasis	B77
Ii14b	G61	Trichuriasis	B79
Ii14c	G62	Hookworm disease (Ancylostomiasis and necatoriasis)	B76
Ii14d	G63	Other intestinal nematode infections	B68, B70-B71, B78, B80-B81
Ij	G64	Other infectious diseases	A20-A32 (except A28.9), A38, A42-A49 (except A48.0, A48.3, A49.9), A65-A70, A74-A79 (except A74.0), A81, A88-A89, A92-A94, A96-B00, B02-B04, B07-B09, B25, B27-B49, B58-B64, B66, B74.3, B74.4, B74.8, B74.9, B75, B83-B88 (except B83.9), B92, B95.0, B95.1, B95.2, B95.3, B95.4, B95.5, B95.6, B95.7, B95.8, B97, N30, N34, N39.0, P35 (except P35.0, P35.3, P35.8), P37 (except P37.0, P37.3, P37.4)
Ij1	G65	Leprosy	A30, B92
Ij2	G66	Urinary tract infections	N30, N34, N39.0
Ij3	G67	Other infectious diseases	A20-A28 (except A28.9), A31-A32, A38, A42-A49 (except A48.0, A48.3, A49.9), A65-A70, A74-A79 (except A74.0), A81, A88-A89, A92-A94, A96-B00, B02-B04, B07-B09, B25, B27-B49, B58-B64, B66, B74.3, B74.4, B74.8, B74.9, B75, B83-B88 (except B83.9), B95-B97, P35 (except P35.0, P35.3, P35.8), P37 (except P37.0, P37.3, P37.4)

GBD 2005 STUDY OPERATIONS MANUAL – FINAL JANUARY 2009

IK	G68	Respiratory infections	H65-H66, J00-J22, J85, P23
IK1	G69	Lower respiratory infections	J09-J22, J85, P23
IK1a	G70	Influenza	J09-J11
IK1b	G71	Pneumococcal pneumonia	J13
IK1c	G72	Haemophilus influenzae type B (Hib) pneumonia	J14
IK1d	G73	Respiratory syncytial virus (RSV) pneumonia	J12.1
IK1e	G74	Other lower respiratory infections	J12 (except J12.1), J15-J22, J85, P23
IK2	G75	Upper respiratory infections	J00-J06
IK3	G76	Otitis media	H65-H66
IL	G77	Maternal conditions	O00-O99
IL1	G78	Maternal haemorrhage	O20, O44-O46, O67, O72
IL2	G79	Maternal sepsis	O85-O86
IL3	G80	Hypertensive disorders of pregnancy	O10-O16
IL4	G81	Obstructed labour	O64-O66
IL5	G82	Abortion	O00-O08
IL6	G83	Other maternal conditions	O21-O43, O47-O63, O68-O71, O73-O84, O87-O99
IM	G84	Neonatal conditions	P00-P22, P24-P29, P36, P38-P94, P96 (except P96.9)
IM1	G85	preterm birth complications	P05-P07, P22, P25-P28, P77
IM2	G86	Birth asphyxia (intrapartum related) and birth trauma	P02-P03, P10-P21, P24
IM3	G87	Sepsis and other infectious conditions of the newborn	P36, P38-P39
IM4	G88	Other non-infectious conditions arising in the perinatal period	P00-P01, P04, P08, P29, P50-P76, P78-P94, P96 (except P96.9)
IN	G89	Nutritional deficiencies	D50-D53, D64.9, E00-E02, E40-E63, E64.0, E64.1, E64.2, E64.3
IN1	G90	Protein-energy malnutrition	E40-E46, E64.0
IN2	G91	Iodine deficiency	E00-E02
IN3	G92	Vitamin A deficiency	E50, E64.1
IN4	G93	Iron-deficiency anaemia	D50, D64.9
IN5	G94	Other nutritional disorders	D51-D53, E51-E63, E64.2, E64.3
II	G95	Noncommunicable diseases	C00-C13, C15-C25, C30-C38, C40-C54, C56-C75 (except C57.9, C63.9, C68.9, C75.9), C77-C79, C81-D48 (except D09.9, D37.9, D38.6, D39.9, D40.9, D41.9, D48.9), D55-D64 (except D64.9), D66-D89, E03-E13, E15-E34, E65-E67, E70-E85 (except E85.3, E85.4, E85.8, E85.9), E88-F98 (except E88.9),

GBD 2005 STUDY OPERATIONS MANUAL – FINAL JANUARY 2009

			G06-G08, G10-G72, G90-G91 (except G91.1, G91.3, G91.8), G93-H61 (except G93.1, G93.2, G93.3, G93.4, G93.5, G93.6), H68-I09, I11-I13, I20-I25, I27-I42 (except I27.1, I31.2, I31.3), I47-I48, I60-I67, I69.0, I69.1, I69.2, I69.3, I71-I73, I77-I80, I82-I84, I86-I98, J30-J70, J82-J84, J92, J93.0, J93.1, J95, J98-K63 (except J98.1, J98.2, J98.3, J98.9), K70, K73-K74, K75.2, K75.3, K75.4, K76-M85 (except K92.0, K92.1, K92.2, K92.9), M87-N15, N20-N28, N31-N32, N35-N64 (except N39.0), N75-N98, Q00-Q99 (except Q89.9, Q99.9), X45
IIA	G96	Malignant neoplasms	C00-C13, C15-C25, C30-C38, C40-C54, C56-C75 (except C57.9, C63.9, C68.9, C75.9), C77-C79, C81-C97
IIA1	G97	Mouth cancer	C00-C08
IIA2	G98	Nasopharynx cancer and other pharynx cancers	C09-C13
IIA2a	G98.1	Nasopharynx cancer	C11
IIA2b	G98.2	Other part of pharynx and oropharynx	C09-C10, C12-C13
IIA3	G99	Oesophagus cancer	C15
IIA4	G100	Stomach cancer	C16
IIA5	G101	Colon and rectum cancers	C18-C21
IIA6	G102	Liver cancer	C22
IIA7	G103	Neoplasm of gallbladder and biliary tract	C23-C24
IIA8	G104	Pancreas cancer	C25
IIA9	G105	Larynx cancer	C32
IIA10	G106	Trachea, bronchus and lung cancers	C33-C34
IIA11	G107	Melanoma of skin	C43
IIA12	G108	Non-melanoma skin cancer	C44
IIA13	G109	Breast cancer	C50
IIA14	G110	Cervix uteri cancer	C53
IIA15	G111	Corpus uteri cancer	C54
IIA16	G112	Ovary cancer	C56
IIA17	G113	Prostate cancer	C61
IIA18	G114	Testicular cancer	C62
IIA19	G115	Kidney and other urinary organ cancers	C64-C66, C68 (except C68.9)
IIA20	G116	Bladder cancer	C67
IIA21	G117	Brain and nervous system cancers	C70-C72
IIA22	G118	Thyroid cancer	C73

GBD 2005 STUDY OPERATIONS MANUAL – FINAL JANUARY 2009

IIA23	G119	Hodgkin lymphoma	C81
IIA24	G120	Non-Hodgkin lymphoma	C82-C85, C96
IIA25	G121	Multiple myeloma	C88-C90
IIA26	G122	Leukaemia	C91-C95
IIA27	G123	Other malignant neoplasms	C17, C30-C31, C37-C38, C40-C41, C45-C49, C51-C52, C57-C60 (except C57.9), C63 (except C63.9), C69, C74-C75 (except C75.9), C77-C79, C97
IIB	G124	Other neoplasms	D00-D48 (except D09.9, D37.9, D38.6, D39.9, D40.9, D41.9, D48.9)
IIC	G125	Diabetes mellitus	E10-E13
IIC1	G126	Insulin-dependent diabetes	E10
IIC2	G127	Non-insulin-dependent diabetes	E11-E13
IID	G128	Endocrine, nutritional, blood and immune disorders	D55-D64 (except D64.9), D66-D89 (except D86.0, D86.2, D86.9), E03-E07, E15-E34, E65-E67, E70-E85 (except E85.3, E85.4, E85.8, E85.9), E88 (except E88.9)
IID1	G129	Haemolytic anaemias	D55-D59
IID1a	G129.1	Thalasseмии	D56
IID1b	G129.2	Sickle cell disorders	D57
IID1c	G129.3	G6PD deficiency	D55
IID1d	G129.4	Other haemolytic anaemias	D58-D59
IID2	G130	Aplastic and other non-nutritional anaemias	D60-D64 (except D64.9)
IID3	G131	Other endocrine, nutritional, blood and immune disorders	D66-D89 (except D86.0, D86.2, D86.9), E03-E07, E15-E34, E65-E67, E70-E85 (except E85.3, E85.4, E85.8, E85.9), E88 (except E88.9)
IIE	G132	Mental and behavioural disorders	F04-F98, X45
IIE1	G133	Unipolar depressive disorders	F32-F33, F34.1
IIE2	G134	Bipolar affective disorder	F30-F31
IIE3	G135	Schizophrenia	F20-F29
IIE4	G136	Alcohol use disorders	F10, X45
IIE5	G137	Drug use disorders	F11-F16, F18-F19
IIE5a	G138	Opioids	F11
IIE5a	G139	Cocaine	F14
IIE5a	G140	Stimulants	F15
IIE5a	G141	Cannabis	F12
IIE5a	G142	Other drug use disorders	F13, F16, F18-F19
IIE6	G143	Anxiety disorders	F40-F44

GBD 2005 STUDY OPERATIONS MANUAL – FINAL JANUARY 2009

IIIE7	G144	Eating disorders	F50
IIIE8	G145.1	Pervasive development disorders	F84.0, F84.1, F84.5, F84.8, F84.9, F88-F89
IIIE8a	G145.2	Autism	F84.0
IIIE8b	G145.3	Asperger's syndrome	F84.5
IIIE8c	G145.4	Other development disorders	F84.1, F84.8, F84.9, F88-F89
IIIE9	G145.5	Childhood behavioural disorders	F90-F92
IIIE9a	G145.6	Attention-Deficit Hyperactivity Disorder (ADHD)	F90
IIIE9b	G145.7	Conduct disorder	F91-F92
IIIE10	G146	Mental retardation not included as sequelae elsewhere	F70-F79
IIIE11	G147	Other mental and behavioral disorders	F04-F09, F17, F34-F39 (except F34.1), F45-F48, F51-F69, F80-F84 (except F84.0, F84.1, F84.5, F84.8, F84.9), F93-F98
IIIF	G148	Neurological conditions	F01-F03, G06-G08, G10-G72, G90-G91 (except G91.1, G91.3, G91.8), G93-G98 (except G93.1, G93.2, G93.3, G93.4, G93.5, G93.6)
IIIF1	G149	Alzheimer's disease and other dementias	F01-F03, G30-G31
IIIF2	G150	Parkinson's disease	G20-G21
IIIF3	G151	Epilepsy	G40-G41
IIIF4	G152	Multiple sclerosis	G35
IIIF5	G153	Migraine	G43
IIIF6	G154	Non-migraine headache	G44
IIIF7	G155	Other neurological conditions	G06-G08, G10-G12, G23-G25, G36-G37, G45-G72, G90-G91 (except G91.1, G91.3, G91.8), G93-G98 (except G93.1, G93.2, G93.3, G93.4, G93.5, G93.6)
IIIG	G156	Sense organ diseases	H00-H61, H68-H93
IIIG1	G157	Glaucoma	H40
IIIG2	G158	Cataracts	H00-H61, H68-H93
IIIG3	G159	Macular degeneration	H35.3
IIIG4	G160	Refraction and accommodation disorders	H49-H52
IIIG5	G161	Hearing loss not due to other diseases or injuries	H90-H91
IIIG6	G162	Other vision loss	H30-H35 (except H35.3), H53-H54
IIIG7	G163	Other sense organ disorders	H00-H21, H27, H43-H47, H55-H61, H68-H83, H92-H93
IIIH	G164	Cardiovascular and circulatory diseases	I00-I09, I11-I13, I20-I25, I27-I42

GBD 2005 STUDY OPERATIONS MANUAL – FINAL JANUARY 2009

			(except I27.1, I31.2, I31.3), I47-I48, I60-I67, I69.0, I69.1, I69.2, I69.3, I71-I73, I77-I80, I82-I84, I86-I98
IIIH1	G165	Rheumatic heart disease	I00-I09
IIIH2	G166	Hypertensive heart disease	I11-I13
IIIH3	G167	Ischaemic heart disease	I20-I25
IIIH4	G168	Cerebrovascular diseases	I60-I67, I69.0, I69.1, I69.2, I69.3
IIIH4a	G169	Ischaemic stroke	I63-I67, I69.3
IIIH4b	G170	Haemorrhagic and other non-ischaemic stroke	I60-I62, I69.0, I69.1, I69.2
IIIH5	G171	Pericarditis, endocarditis and myocarditis	I30-I33 (except I31.2, I31.3), I38-I40
IIIH6	G172	Cardiomyopathy	142
IIIH7	G173	Conduction disorders and other dysrhythmias	I47-I48
IIIH8	G174	Aortic aneurysm	171
IIIH9	G175	Peripheral vascular disease	173
IIIH10	G176	Other circulatory diseases	I27-I28 (except I27.1), I34-I37, I72, I77-I80, I82-I84, I86-I98
IIIi	G177	Respiratory diseases	D86.0, D86.2, D86.9, J30-J70, J82-J84, J92, J93.0, J93.1, J95, J98 (except J98.1, J98.2, J98.3, J98.9)
IIIi1	G178	Chronic obstructive pulmonary disease	J40-J44
IIIi2	G178.1	Pneumoconiosis	J60-J65
IIIi3	G179	Asthma	J45-J46
IIIi4	G179.1	Other interstitial lung disease	D86.0, D86.2, D86.9, J84
IIIi5	G180	Other respiratory diseases	J30-J39, J47, J66-J70, J82, J92, J93.0, J93.1, J95, J98 (except J98.1, J98.2, J98.3, J98.9)
IIJ	G181	Digestive diseases	K20-K63, K70, K73-K74, K75.2, K75.3, K75.4, K76-K92 (except K92.0, K92.1, K92.2, K92.9)
IIJ1	G182	Peptic ulcer disease	K25-K27
IIJ2	G183	Appendicitis	K35-K37
IIJ3	G184	Intestinal obstruction and strangulated hernias	K40-K46, K56
IIJ4	G185	Noninfective inflammatory bowel disease	K50-K52
IIJ5	G186	Vascular insufficiency of intestine	K55
IIJ6	G187	Cirrhosis of the liver	K70, K73-K74
IIJ7	G188	Gall bladder and bile duct disease	K80-K83
IIJ8	G189	Pancreatitis	K85-K86
IIJ9	G190	Other digestive diseases	K20-K22, K28-K31, K38, K57-K63, K75.2, K75.3, K75.4, K76-

GBD 2005 STUDY OPERATIONS MANUAL – FINAL JANUARY 2009

			K77, K90-K92 (except K92.0, K92.1, K92.2, K92.9)
IIK	G191	Genitourinary diseases	N00-N15, N20-N28, N31-N32, N35-N64 (except N39.0), N75-N98
IIK1	G192	Acute and chronic glomerulonephritis	N00-N08
IIK2	G193	Acute and chronic pyelonephritis and tubulointerstitial nephritis	N10-N12
IIK3	G194	Urolithiasis	N20-N21
IIK4	G195	Benign prostatic hypertrophy	N40
IIK5	G196	Primary infertility	N46, N97
IIK6	G197	Other urinary diseases	N13-N15, N23-N28, N31-N32, N35-N39 (except N39.0), N41-N45, N47-N50
IIK7	G198	Other gynecological disorders	N60-N64, N75-N96, N98
III	G199	Skin diseases	L00-L98
III1	G200	Eczema	L20-L30
III2	G201	Psoriasis	L40-L41
III3	G202	Other skin and subcutaneous diseases (infective)	L00-L08
III4	G203	Other skin and subcutaneous diseases (noninfective)	L10-L13, L42-L98
IIM	G204	Musculoskeletal diseases	M00-M85, M87-M99
IIM1	G205	Rheumatoid arthritis	M05-M06
IIM2	G206	Osteoarthritis	M15-M19
IIM3	G207	Back pain	M46.9, M47, M48.0, M48.1, M48.2, M48.8, M48.9, M50-M54
IIM4	G208	Gout	M10
IIM5	G209	Other musculoskeletal disorders	M00-M02, M08, M11-M13, M20-M46 (except M46.9), M48 (except M48.0, M48.1, M48.2, M48.8, M48.9), M60-M85, M87-M99
IIN	G210	Congenital anomalies	Q00-Q99 (except Q89.9, Q99.9)
IIN1	G211	Neural tube defects	Q00, Q03, Q05
IIN2	G212	Congenital heart anomalies	Q20-Q28
IIN3	G213	Cleft lip and cleft palate	Q35-Q37
IIN4	G214	Digestive system malformations	Q38-Q45
IIN5	G215	Urogenital malformations	Q50-Q64
IIN6	G216	Fetal alcohol syndrome	Q86.0
IIN7	G217	Down's syndrome	Q90
IIN8	G218	Other chromosomal abnormalities	Q91-Q99 (except Q99.9)
IIN9	G219	Other congenital anomalies	Q01-Q02, Q04, Q06-Q18, Q30-Q34, Q65-Q89 (except Q86.0, Q89.9)
IIO	G220	Oral conditions	K00-K14

GBD 2005 STUDY OPERATIONS MANUAL – FINAL JANUARY 2009

IIO1	G221	Dental caries	K02
IIO2	G222	Periodontal disease	K05
IIO3	G223	Edentulism	
IIO4	G224	Other oral diseases	K00-K01, K03-K04, K06-K14
III	G225	Injuries	V01-V98, W00-X44, X46-X58, X60-Y09, Y35-Y84, Y85.0, Y87.0, Y87.1, Y88, Y89.0, Y89.1
IIIA	G226	Unintentional injuries	V01-V98, W00-W52, W65-W74, X00-X19, X34-X44, X46-X49, Y40-Y84, Y85.0, Y88
IIIA1	G227	Transport injuries	V01-V98, Y85.0
IIIA1a	G228	Road traffic injuries	V01-V04, V06-V79, V85.0, V87, V89, Y85.0
IIIA1a1	G229	a1. Injured pedestrian	V01-V04, V06-V09
IIIA1a2	G230	a2. Injured from vehicle collision	V10-V79, V85.0, V87, V89, Y85.0
IIIA1b	G231	Other transportation injuries	V05, V80-V86 (except V85.0), V88, V90-V98
IIIA2	G232	Poisonings	X40-X44, X46-X49
IIIA3	G233	Falls	W00-W19
IIIA4	G234	Fires, heat, and hot substances	X00-X19
IIIA5	G235	Drowning	W65-W74
IIIA6	G236	Exposure to mechanical forces	W20-W52
IIIA6a	G237	Machinery accidents	W28-W31
IIIA6b	G238	Other mechanical accident	W20-W27, W32-W52
IIIA7	G239	Natural disasters	X34-X39
IIIA8	G240	Adverse effects of medical treatment	Y40-Y84, Y88
IIIA9	G241	Injuries due to animal bites or contact with a marine animal	W53-W64, X20-X29
IIIA10	G242	Other unintentional injuries	W75-W99, X30-X33, X50-X58
IIIB	G243	Intentional injuries	X60-Y09, Y35-Y36, Y87.0, Y87.1, Y89.0, Y89.1
IIIB1	G244	Self-inflicted injuries	X60-X84, Y87.0
IIIB2	G245	Interpersonal violence	X85-Y09, Y87.1
IIIB3	G246	Collective violence	Y36, Y89.1
IIIB4	G247	Legally sanctioned deaths	Y35, Y89.0

GBD 2005 STUDY OPERATIONS MANUAL – FINAL JANUARY 2009

Description (type of Garbage Codes)		ICD10 Codes
Garbage code (1.1)	Causes that cannot lead to death - redistribute on all causes	R00-R01, R03-R17, R19-R54 (except R40.2), R56 (except R56.0), R59-R63, R68-R99
Garbage code (1.2)	Causes that cannot lead to death - redistribute on some causes	R40.2, R55, R56.0, R57-R58, R64
Garbage code (2.1)	Malignant or non malignant neoplasm without specification of any site	C80, D09.9
Garbage code (2.2)	Malignant or non malignant neoplasm with specification of organ system	C14, C26, C39, C55, C57.9, C63.9, C68.9, C75.9
Garbage code (2.3)	Malignant or non malignant neoplasm with specification of area of body	C76
Garbage code (2.4)	Carcinoma in situ, unknown behaviour neoplasms as a cause of death or benign neoplasms	D37.9, D38.6, D39.9, D40.9, D41.9, D48.9
Garbage code (3.1)	Unspecified diseases and injuries in one chapter	B99, E88.9, F99-G00 (except G00.0, G00.1, G00.2, G00.3, G00.8, G00.9), I51, I99, J98.9, K92.9, P95, P96.9, Q89.9, Q99.9
Garbage code (3.2)	Unspecified diseases and injuries in some part of one chapter or in diseases group	A28.9, A49.9, A64, B82, B83.9, B89, E14, V99, X59, Y10-Y34
Garbage code (4)	Intermediate cause in death chain	A40-A41, A48.0, A48.3, E85.3, E85.4, E85.8, E85.9, E86-E87, G91.1, G91.3, G91.8, G92, G93.1, G93.2, G93.3, G93.4, G93.5, G93.6, I26, I27.1, I31.2, I31.3, I44-I45, I49-I50, I74, I81, I85, J80-J81, J86-J90, J93-J94 (except J93.0, J93.1), J98.1, J98.2, J98.3, K65-K66, K71-K72, K75 (except K75.2, K75.3, K75.4), K92.0, K92.1, K92.2, M86, N17-N19, R02, R18, S00-T98
Garbage code (5)	Sequelae as an intermediate cause or as contemporary conditions besides another intermediate cause	B94 (except B94.0, B94.1), E64 (except E64.0, E64.1, E64.2, E64.3), E68, G09, G80-G83, I69 (except I69.0, I69.1, I69.2, I69.3), Y85-Y87 (except Y85.0, Y87.0, Y87.1), Y89 (except Y89.0, Y89.1)

GBD 2005 STUDY OPERATIONS MANUAL – FINAL JANUARY 2009

Garbage code (6)	Immediate cause of death or mode of death	D65, I46, J96
Garbage code (7)	Particular garbage codes	I10, I15, I70
Garbage	All garbage codes	A28.9, A40-A41, A48.0, A48.3, A49.9, A64, B82, B83.9, B89, B94-B96 (except B94.0, B94.1, B95.0, B95.1, B95.2, B95.3, B95.4, B95.5, B95.6, B95.7, B95.8), B99, C14, C26, C39, C55, C57.9, C63.9, C68.9, C75.9, C76, C80, D09.9, D37.9, D38.6, D39.9, D40.9, D41.9, D48.9, D65, E14, E64 (except E64.0, E64.1, E64.2, E64.3), E68, E85.3, E85.4, E85.8, E85.9, E86-E87, E88.9, F99-G00 (except G00.0, G00.1, G00.2, G00.3, G00.8, G00.9), G09, G80-G83, G91.1, G91.3, G91.8, G92, G93.1, G93.2, G93.3, G93.4, G93.5, G93.6, I10, I15, I26, I27.1, I31.2, I31.3, I44-I46, I49-I51, I69-I70 (except I69.0, I69.1, I69.2, I69.3), I74, I81, I85, I99, J80-J81, J86-J90, J93-J94 (except J93.0, J93.1), J96, J98.1, J98.2, J98.3, J98.9, K65-K66, K71-K72, K75 (except K75.2, K75.3, K75.4), K92.0, K92.1, K92.2, K92.9, M86, N17-N19, P95, P96.9, Q89.9, Q99.9, R00-T98, V99, X59, Y10-Y34, Y85-Y87 (except Y85.0, Y87.0, Y87.1), Y89-A28.9 (except Y89.0, Y89.1)

NOTES

- 1 For cause of death analysis certain ICD codes are considered garbage codes and are distributed using empirical algorithms. Table 1 at the end of Chapter 11 lists these redistributable garbage codes.
- 2 For countries with 4-digit ICD-10 codes, a more detailed list is being developed.

RISK FACTORS

Unlike diseases and injuries for which there is a relatively coherent classification system, there is an infinitely large number of risk factors, traditionally defined in different scientific disciplines. We have used the following principles, in consultation with disease, injury, and risk factor experts, to develop the initial list of risk factors for the CRA component of the GBD 2005 Study:

- Risk factors should be potentially modifiable or as in the case of genetic screening, can lead to modifications in harm due to changes in healthcare use.
- Risks should be assessed irrespective of place in a causal chain or scientific discipline that has traditionally analyzed the risk factor, as long as evidence of causal effect can be established.
- Risks are defined to be not too broad (e.g. diet or environment as a whole) or too narrow (e.g. every single fruit and vegetable or every toxicant in tobacco smoke), with a relatively specific definition of risk factor exposure.
- Protective as well as hazardous factors are considered. However, the absence of a specific intervention should not be assessed as a risk factor as part of the GBD 2005 Study, but rather in the measurement of intervention coverage and effectiveness.
- Sufficient data exist on risk factor exposure and risk-factor disease relationships.

The current intended risk factor list, which is based on the above criteria, is provided in Table 2. Like in the case of disease and injury causes, we have used a tree structure for risk factor classification.

TABLE 2 GBD STUDY RISK FACTOR LIST

Risk Factor Category	Risk Factor
Addictive substances	Alcohol use
	Illicit drug use
	Tobacco use
Environmental risk factors	Urban ambient air pollution
	Household air pollution from solid fuel use
	Passive smoking / Environmental tobacco smoke ¹
	Food contamination (biological and chemical)
	Unsafe water, sanitation, hygiene (biological and chemical)
	Lead exposure

	Road and vehicle safety (TBC)
Occupational risk factors	<p>Airborne particulates</p> <p>Carcinogens</p> <p>Ergonomic stressors</p> <p>Noise</p> <p>Risks for injuries</p> <p>Pesticides</p> <p>Other occupational risks TBD</p>
Violence related risk factors	<p>Sexual violence (including rape and childhood sexual abuse)³</p> <p>Intimate partner violence</p> <p>Collective violence</p> <p>Possession of firearms (TBC)</p>
Metabolic, nutritional, and lifestyle risks for chronic diseases	<p>High blood glucose</p> <p>High blood pressure</p> <p>High cholesterol</p> <p>High body mass index (BMI)</p> <p>Low intake of fruit and vegetable</p> <p>High dietary sodium (salt)</p> <p>Dietary fats (protective and hazardous effects of subtypes)</p> <p>Other nutritional risks TBD</p> <p>Physical inactivity</p>
Undernutrition (primarily child and maternal)³	<p>Folic acid deficiency</p> <p>Anaemia and/or iron deficiency</p> <p>Small-for-gestational-age</p> <p>Growth retardation (stunting and wasting)</p> <p>Suboptimal breastfeeding</p> <p>Vitamin A deficiency</p> <p>Zinc deficiency</p>
Reproductive and sexual risk	Unwanted pregnancies

factors	Unsafe sex
Risks related to medical practice	TBD
Genetic risk factors	TBD
Systemic risk factors	Global climate change Socioeconomic factors (specific factors TBD)
Other risk factors	Osteoporosis ²

NOTES

- 1 To be analyzed in close coordination with work on tobacco use.
- 2 Included as risk factors, and not as “disease as risk” because direct burden not estimated among diseases.
- 3 Note that a risk factor, once defined, cannot be restricted to a particular age group and must be assessed across ages when evidence for hazardous or protective effects exists.

DISEASES ALSO TREATED AS RISK FACTORS

In the GBD research to date, disease and injury burden has been reported according to categorical attribution, primarily following the ICD system, and risk factor burden - according to counterfactual attribution. The categorical attribution has implications for diseases such as malaria, hepatitis B, diabetes, and depression. Each of these diseases is a risk factor for mortality or disability from other ICD causes because categorical attribution may underestimate the importance of the condition. A complete shift to counterfactual attribution, while being the most comparable approach, deviates from the accepted medical protocols and is also problematic for users. Users, particularly those less versed in the tradition of counterfactual estimation, want the sum of cause-specific figures to equal the total number of deaths or DALYs.

It is conceivable to develop a compromise “re-distribution” approach where cause-specific deaths or burden sum to all-cause deaths or burden, but the correlation with counterfactual estimates would be 1.0. Such an approach would require extensive communication and education of the user community, including those familiar with the current clinical classifications which are categorical. As a practical solution the GBD 2005 Study will continue to use categorical attribution of deaths and DALYs to disease and injury causes. It will also treat a selected number of diseases and injuries as risk factors for other diseases and injuries using counterfactual estimation and the CRA methods (see Chapter 18). The selected “diseases as risk factors” include those with strong etiological relationships. They are listed below.

- Tuberculosis
- STDs excluding HIV

- Diarrhoeal diseases
- Hepatitis B and C
- Malaria
- Chagas disease
- Schistosomiasis
- Prematurity
- Diabetes mellitus
- Unipolar depressive disorders
- Selected other mental and behavioural disorders (anxiety disorders, schizophrenia, bipolar affective disorder, alcohol use disorders and drug use disorders)

PROCESS FOR REVIEWING AND REVISING THE DISEASE/INJURY AND RISK FACTOR CAUSE LISTS

The disease and injury cause list and the risk factor lists shown here are provisional, prepared in accordance with the principles described above, and based on the previous GBD and CRA projects and preliminary discussions of the Core Team with experts in the field. Revisions, deletions and additions to these lists are possible as described below but will be evaluated to ensure consistency with the selection principles. In addition, proposals will have to be consistent with the practical issue of finding an Expert Group willing and able to undertake the work required by the proposed changes or additions.

REVIEWING AND REVISING THE DISEASE AND INJURY CAUSE LIST

The first task of each Expert Group is to review the disease and injury cause list, with a particular focus on the diseases and injury groups for which they are undertaking epidemiological assessments. Once the GBD 2005 Study has reached the stage of database tools development and cause of death analyses, it will be difficult or impossible to revise the categories (and associated ICD codes) included in the disease and injury cause list.

Proposed revisions must adhere to the GBD principles outlined above. They should consider that a revision to the cause list implies that deaths due to that cause can and will need to be estimated for all regions, and that incidence and other inputs for YLD calculation will need to be estimated by age and sex in all regions. The proposed changes will be evaluated for feasibility of implementation by the Cause of Death and Disability Weights Sub-teams. Expert Groups should also keep in mind the need to choose sequelae and develop case and sequela definitions. Subcategories of disease cases or sequelae should not be proposed as separate causes in the disease and injury list (e.g. retinopathy of prematurity, acute and chronic cases of a disease), unless they can be justified as separate disease entities with the possibility to categorically assign deaths to them. Thus, ischaemic and haemorrhagic stroke are proposed as separate disease categories but diabetic neuropathy and diabetic retinopathy are not.

Any proposed revisions should state the recommended modification to the GBD cause categories as well as the ICD-10 codes corresponding to the categories, and provide a brief justification for the suggested change and an assessment of its feasibility for the GBD 2005 Study.

REVIEWING AND REVISING THE RISK FACTOR AND DISEASE-AS-RISK-FACTOR LIST

The risk factors listed above cover important health hazards. Arguably there are hundreds of exposures that are harmful to health. We selected a relatively small number of exposures for quantification, largely determined by the availability of data about their prevalence as well as their expected health effects in different parts of the world. It was also important to make choices about the precise definition and division of risk factors (e.g. inclusion of water, sanitation and hygiene as a single risk factor versus separate inclusion of urban ambient air pollution and lead exposure) that reflect the potential for satisfactory quantification of their population exposure distributions and health effects using the existing scientific evidence and available data.

Each Expert Group should review the risk factor list. Suggested additions and revisions should provide a brief justification, a relatively precise definition of risk factor exposure and the variable used to measure it, and a description of data availability for measuring exposure in different regions and of epidemiological and other evidence that allows quantifying risk factor hazardous effects.

Revision of the list of diseases which are assessed as risk factors will follow a similar process to the revision of the risk factors' list. For the GBD 2005 Study the addition of new diseases as risk factors should be restricted to the diseases with a strong *etiological* relationship (for example as incorporated in a natural history model) to other conditions presented separately in the GBD disease and injury cause list.

REFERENCES

- (1) Murray CJL, Lopez AD. *The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020*. Cambridge, Harvard University Press on behalf of the World Health Organization and the World Bank, 1996.
- (2) World Health Organization. *International statistical classification of diseases and related health problems*, Tenth Revision (ICD-10). Geneva, World Health Organization, 1992.

PROCESS FOR REVISIONS TO GBD CAUSE LISTS

The Expert Groups may develop proposals for adding causes to the GBD disease and injury cause list or the risk factor cause list, as well as for revising the ICD codes associated with disease and injury causes.

DISEASE AND INJURY CAUSE LIST

Review the disease and injury cause list, with a particular focus on the diseases and injury groups for which you are undertaking epidemiological assessments.

If you wish to propose a change to the list in accordance with the GBD principles outlined above, submit a proposal to the Core Team that includes:

- summary of proposed revision to the GBD cause categories;
- ICD-10 codes corresponding to the categories;
- a brief justification for the proposed change;
- an assessment of the feasibility of making estimates for the GBD 2005 Study;
- the name of the Expert Group proposing to carry out the estimates.

RISK FACTOR LIST AND DISEASES-AS-RISKS LIST

Review the risk factor list and the diseases as risks list with a particular focus on the risks that your Expert Group is addressing.

To recommend additions or changes, submit a proposal to the Core Team that includes:

- a brief justification;
- a relatively precise definition of risk factor exposure and the variable used to measure it;
- a description of the data availability for measuring exposure in different regions and of epidemiological and other evidence that allows quantifying risk factor hazardous effects;
- the name of the Expert Group proposing to carry out the estimates

CHAPTER 14

SEQUELAE DEFINITIONS AND SELECTION CRITERIA

INTRODUCTION

The analytic framework for estimating YLD (the non-fatal component of the DALY) is the grouping of non-fatal health consequences resulting from the incidence of disease or injury incident causes into a set of discrete case and sequela categories. The conceptual framework for these was outlined in Chapter 12. This chapter summarizes the process and criteria for selection of disease and injury sequelae for the GBD 2005 Study; provides a list of the most recent case and sequela definitions used in the GBD 2001 and 2002 (1); and outlines the process for review and revision of this cause list by the Expert Groups.

Injury categories in the GBD 2005 Study cause list are defined in terms of groups of external causes of injury (see Chapter 13). In the GBD analyses to date, all injury cause groups are considered to have a large set of “nature of injury” sequelae (e.g. road traffic injury as an external cause may result in fractures, brain injury, burns, drowning, crushing injuries, etc. as sequelae). The injury sequelae set is the same for all external causes (see below). The following section thus focuses on the process and criteria for selection of disease sequelae.

SELECTING AND DEFINING GBD DISEASE SEQUELAE

The GBD links losses of health to disease and injury causes through the concepts of cases and sequelae. For incident cases of a given disease or injury in the population, there will be a distribution of current and future health states (conceptualized in terms of functioning in a set of health domains) in the population, and the GBD maps this distribution of health states to a small set of discrete entities for which epidemiological estimates and YLD calculations are made. The GBD uses the term “sequela” as an umbrella term to describe this set of discrete entities. As noted in Chapter 12, our use of the term “sequela” encompasses not only the traditional clinical meaning, but also a broader categorization of health outcomes such as severity levels for a particular impairment.

For a given disease or injury cause, the choice and definition of cases and sequelae are based on an understanding of the natural history of the disease, identification of the paths and components in that history associated with significant loss of functioning (versus those that are only etiological relevant), and the types, and the availability of data to estimate incidence, prevalence and transition rates. This requires good understanding of the epidemiology of the disease and the availability of population-level data.

In order to decide on the sequelae required for the estimation of YLD for a disease, the following steps are followed:

1. Identify the scope of the cause category for the disease: are there several disease entities which may need to be treated differently, or is there only one fairly homogeneous disease category causing most loss of health?
2. Review current knowledge of the disease and develop/review the case definition.
3. Construct a diagram of the natural history of the disease.
4. Identify the main pathways to health states comprising significant loss of health (non-trivial severity and/or high prevalence).
5. Develop definitions for each of the sequelae taking into account that epidemiological data will need to be found in the systematic reviews that conform with these definitions.

In most cases, the choice of disabling sequelae to be included in the GBD 2005 Study will build upon earlier GBD efforts. At the outset, it is important to recognize that it is simply not possible to include *every* disabling sequela for *each* disease treated in our analysis, and as a consequence, some nominal fraction of the total burden might not be captured. In the GBD 1990 Study, for instance, analysis was restricted to five sequelae for diabetes mellitus: diabetes *per se*, retinopathy, neuropathy, diabetic foot, and amputation. Doubtless there are other sequelae for diabetes, just as there are for many other conditions, which will fall outside the scope of the GBD 2005 Study's analysis. While it is important to ensure that the major sequelae for each disease are included, i.e. those resulting in significant loss of health at the population level, it is also important to recognize that the Expert Groups will have limited time and resources, and will not be able to focus on every possible sequela of a particular disease. In many cases, additional sequela, while possibly leading to a more complete model, may not add any consequential increment to the total YLD.

Expert Groups will rely on their understanding of the existing literature on the definition, natural history, classification, severity, and epidemiology of the condition studied and its disabling sequelae. A useful first step is to draw a diagram of the natural history of the disease. Some examples are given in Chapter 16. The next step is to carefully examine the natural history diagram and the set of sequelae chosen in previous GBD analyses (given in Table 1 below) to address the following questions:

- What are the important disabling outcomes for any given disease, particularly long-term outcomes?
- Can these be treated as essentially separate and, if so, can they be estimated separately? Or alternatively, are they bundled together and thus more appropriately treated as a single outcome state?

- Should the sequelae combine all relevant severity levels in a single category or should they be disaggregated into severity levels (e.g. mild, moderate, and severe hearing loss defined as a hearing threshold level in the better ear of between 25 and 44 decibel (dB), between 45 and 64 dB, and greater than 65 dB, respectively) to enable more specific regional information on severity distributions to be used?
- For impairments and other outcomes that may be common sequelae across different causes, are the sequelae chosen using consistent definitions and categories (e.g. cognitive impairment thresholds for mental disability as a sequela of underlying conditions such as congenital malformations, meningitis, head trauma, neonatal conditions or epilepsy)?
- For certain impairments that are sequelae for multiple causes, a Sub-Team will work with relevant Expert Groups to ensure cause-specific prevalence estimates are consistent with the total impairment envelopes at the population level.

The next step is to delineate a precise definition for each sequela in the analysis. The aim is to describe the dynamic of a disease with a parsimonious model that captures the important components of the disease but is not too complex to accommodate epidemiological estimation based on the available data. In some cases, there may be several possible definitions in use. For example:

- Deafness may be measured at non-standard decibel thresholds in some studies vs. standard clinical thresholds.
- Various case definitions for diabetes are now in use: fasting plasma glucose greater than 7mmol/l; haemoglobin A1c greater than 7.0; haemoglobin A1c greater than 6.4, etc.

It is not intended to exclude data by having too strict criteria for the case definitions. The important operating principle is that whatever case definition is adopted, empirical mapping from different case definitions must be developed so that data collected using alternative definitions can be compared. Non-standard definitions can only be used if data can be mapped to the standard GBD definition. In addition to the case definitions, the Expert Groups will be asked to complete standardized descriptions of functional health levels and symptoms associated with each sequela. More details on these standardized descriptions follow in Chapter 15, and the standardized checklist to be used for these descriptions is included as a forthcoming appendix to Chapter 15.

IMPORTANT FEEDBACK LOOP

The case definitions used for sequelae will need to match the case definitions used to derive disability weights. This will require coordination between the Expert Groups, the Cluster Leaders and the Core Team members working on disability weights (see Chapter 15).

ENSURING THAT CERTAIN IMPAIRMENT SEQUELAE ARE CONSISTENT WITH THE OVERALL PREVALENCE OF IMPAIRMENT

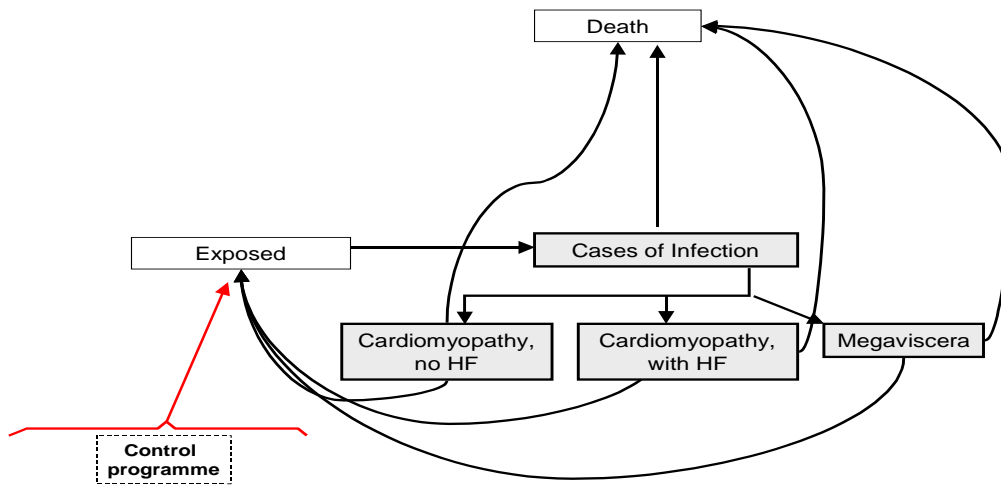
There are a number of impairments that are sequelae for multiple causes, including vision loss, hearing loss, cognitive deficits (IQ decrements, mental retardation etc), and anaemia. Previous versions of the GBD have not attempted to ensure that prevalence estimates for these impairments sum across causes in a way consistent with the available data on total prevalence in populations. The GBD 2005 Study aims to do this and a core subteam will estimate population prevalences for these impairments in consultation with relevant expert groups. An iterative process will ensure a consistent cause distribution for a complete set of causes. In some cases, it will be necessary to have a residual category for impairment not associated with specific GBD causes. The core subteam will also assess the feasibility of extending this approach to other sequelae such as incontinence, seizure disorder and infertility.

EXAMPLES OF GBD DISEASE MODELS AND SEQUELAE

As described in Chapter 12, GBD “sequelae” may include only the disease case, or the disease case and several clinical sequelae, or only several disabling sequelae. Here we provide selected examples illustrating the range of different types of sequelae lists that may pertain to different disease causes.

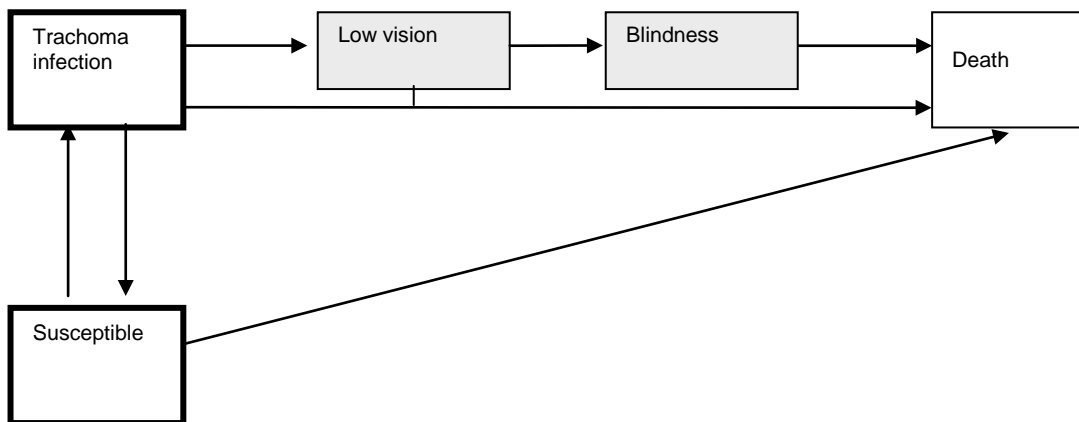
EXAMPLE 1: A DISEASE WITH SEVERAL DISTINCT CLINICAL SEQUELAE THAT MAY OCCUR IN SUBGROUPS OF CASES

Chagas’ disease exists only in the American continent and is caused by a flagellate protozoan parasite, *Trypanosoma cruzi*. There are two stages of the human disease: the acute stage shortly after infection and the chronic stage, which may last several years. These chronic changes include Chagasic myocardiopathy, which may lead to arrhythmia, heart failure and death as well as digestive lesions in the form of megacolon and megaesophagus. The incidence and prevalence of Chagas disease infection were estimated from community studies for the GBD 2001 and 2002. The disease model is shown in the figure below. It was assumed that 4% of cases would develop cardiomyopathy with heart failure, 18% cardiomyopathy without heart failure, and 3% megaviscera. The sequelae used for the estimation of YLD are shown below as the boxes shaded in grey.



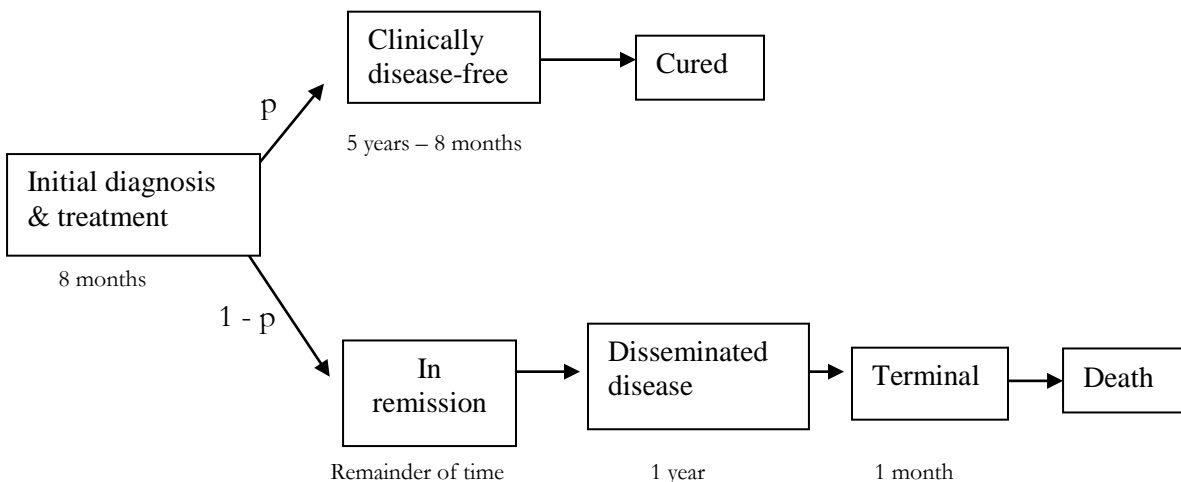
EXAMPLE 2: A DISEASE WHERE ONLY THE DISABLING IMPAIRMENTS ARE TREATED AS SEQUELAE, NOT THE DISEASE CASE ITSELF

The disease model for trachoma is a simple three-box model as shown in the figure below. YLD was calculated for the boxes shaded in grey. Regional prevalences for low vision and blindness caused by trachoma infection were estimated from survey data. The incidence of trachoma infection itself was not estimated. DisMod was used to estimate the incidence of low vision and blindness from the prevalence estimates assuming zero remission and mortality relative risks of 1.5 for low vision and 2.5 for blindness.



EXAMPLE 3: A DISEASE WITH PROGRESSIVE HEALTH STATES AND AT LEAST TWO PATHWAYS

Below is an example of a diagram for a disease with progressive health states. It is a diagram used in the Dutch and Australian Burden of Disease studies for breast cancer with a tumour size greater than 5 cm at diagnosis. Each of the boxes (apart from “Cured” and “Death”) represents disease sequelae used in the analysis of YLD.



NOTES

p = proportion of cases who survive; $1 - p$ = proportion of cases dying
 The period of disability was set to five years in survivors. The average duration of those who die is determined from follow-up data of cancer registry. The durations for initial diagnosis and treatment, disseminated disease and the terminal phase were set after discussions with cancer experts. Each of the health states in the diagram had a separate disability weight.

EXAMPLE 4: A DISEASE WHERE SEQUELAE CHOSEN TO ENABLE MODELING OF THE SEQUELA OF INTEREST

Due to the lack of population-level data on the prevalence and health state distributions of stroke survivors, the GBD 2001 and 2002 used a model in which the incidence and prevalence of 28-day stroke survivors was estimated from the incidence of first-ever stroke, together with estimates of 28-day case fatality rates and long-term excess mortality.

STROKE SEQUELAE USED IN THE GBD 2001 AND 2002

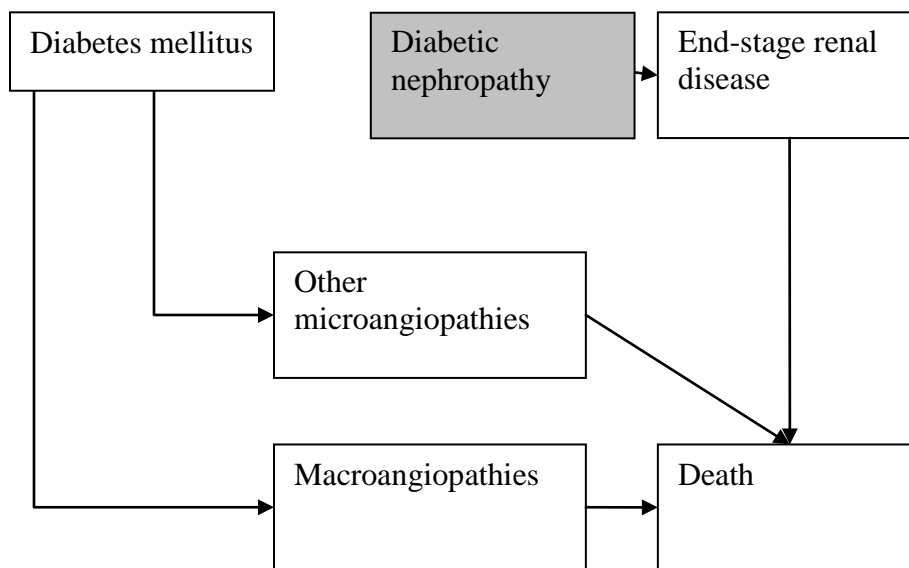
<i>Sequela</i>	<i>Health State Description</i>
-----------------------	--

First ever stroke	First-ever acute stroke event and period immediately following. Severe pain, unable to self-care or carry out usual activities, severe mobility limitations, likely cognitive and motor deficits. The average duration of this period for those who die within 28 days is around 6 days. Model this health state with duration of 6 days for all first strokes.
28-day stroke survivor	Persons who survive at least 28 days after first-ever stroke are estimated from incidence of first-ever stroke and measured 28-day case fatality rates. The model assumes that second and subsequent strokes are included in the average disability weight and mortality risk for this sequela. The model assumes approximately 50% of long-term stroke survivors have long-term disability and the disability weight for this sequela is an average across all survivors, disabled and not disabled.

EXAMPLE 5: PROPOSALS FOR NEW SEQUELAE DEFINITIONS

Diabetes Mellitus

1. Proposal: include in sequelae for diabetes mellitus “Diabetic nephropathy.”
2. Disease model:

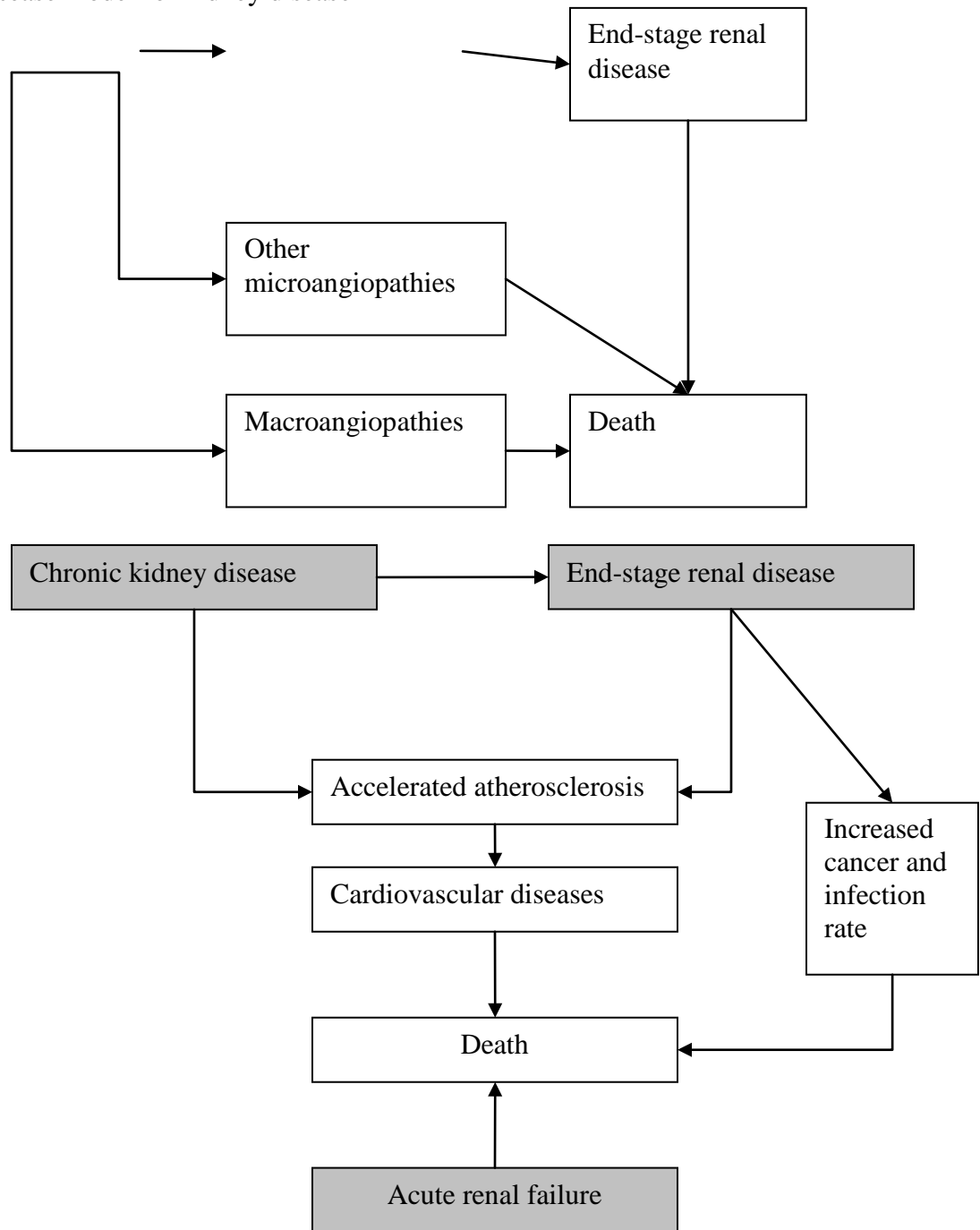


3. Definition: presence of albuminuria (proteinuria) or/and decreased glomerular filtration rate or/and elevated serum creatinine in patients with diabetes mellitus in the absence of other reasons for these findings; or/and specific changes on kidney biopsy.
4. Incidence, prevalence and mortality could be estimated from existing registries and epidemiological surveys.

Kidney Diseases

1. Definition for kidney diseases: presence of albuminuria (proteinuria) and/or hematuria and/or decreased glomerular filtration rate and/or elevated serum creatinine and/or data from biopsy and/or ultrasound.
2. Kidney disease will include: chronic kidney diseases, end-stage renal disease, and acute renal failure.

3. Disease model for kidney disease



4. Incidence, prevalence and mortality could be estimated from existing registries and epidemiological surveys.

PROVISIONAL LIST OF GBD STUDY DISEASE SEQUELAE

Table 1 lists the GBD case and sequela definitions used in the GBD 2001 and 2002 updates (1). Some of these have been updated from the definitions used in the 1990 GBD Study as documented in *Global Health Statistics* (2). New causes included in this GBD Study for the first time do not have existing case and sequela definitions, and these will need to be developed by the Expert Groups.

THE TABLE WILL BE POSTED TO THE GBD WEBSITE (JAN 2009)

PROVISIONAL LIST OF GBD STUDY INJURY SEQUELAE

This section describes the injury case and sequelae definitions developed for the GBD 1990 Study and used for subsequent revisions. An incident episode of a non-fatal injury is defined as an episode that is severe enough for the person to be hospitalized, or which requires emergency room care (if such care is available). Previous burden studies have shown that the main sources of disability from injuries are road traffic accidents, falls, fires, other unintentional injuries and, in some countries, violence and war. The group of “other unintentional injuries” is often a leading cause of YLD in injuries and is comprised of a wide variety of injuries, including being struck or crushed by an object, machinery accidents, and sports injuries. This grouping has been further disaggregated for the GBD 2005 Study. Poisoning, drowning and self-inflicted injuries mainly cause YLL and if disability is incurred, it is usually of short duration and therefore does not contribute significantly to YLD.

The rules of the International Classification of Diseases (ICD) allow for the coding of injuries along two dimensions: according to the external cause of an injury, or according to the physiological damage arising from an injury (Figure 1). The GBD 1990 Study established that disability is estimated most accurately from knowledge of the nature of injury, but that estimates should ultimately be attributed back to a cause for policy relevance.

To facilitate the incorporation of both dimensions analytically, the large number of detailed ICD nature-of-injury codes was collapsed into thirty-three categories in a way that combined similar outcomes. An analysis of health facility data for the GBD 1990 Study with data coded in both dimensions demonstrated that the distribution of these nature-of-injury categories differed both within a given external cause group by age and sex, and between external cause groups. Thus a matrix approach was adopted whereby average distributions of nature-of-injury categories were generated for each cause, age and sex stratum across the countries for which data were analyzed.

**FIGURE 1 ICD AND INJURIES:
A TWO-DIMENSIONAL APPROACH**

Cause of injury:	The cause of the bodily harm, e.g. road traffic accident, falls or fires
Nature of injury:	A description of the actual bodily harm caused by the type of injury, e.g. a fractured hip, brain injury or third degree burns over 20% of body surface

Expert opinion provided to the GBD 1990 Study was that some nature-of-injury categories would comprise cases with short-term disability only (e.g. open wounds, fractured arm), while others would be made up of cases all of whom would experience permanent disability (e.g. amputations, spinal cord lesions). A few categories, however, would contain both short- and long-term cases (e.g. head injuries). Due to the paucity of cohort studies on injuries at the time, non-empirical methods were adopted whereby participants at the Geneva meeting on disability weights were asked to use the provided information to estimate the severity of treated and untreated forms of each of the thirty-three nature-of-injury categories, as well as their average duration. Estimates were also derived on the proportion with life-long disability for certain categories (3).

A decision was made early on as part of the GBD 2000 revisions to retain all 1990 disability weights relating to injury on a provisional basis until more refined methods for this aspect of burden of disease estimation are finalized. A practical implication of this decision has been the retention of the thirty-three nature-of-injury categories without modification, including the distinction between short- and long-term disabilities within some categories. The generation of new weights for injuries is the obvious point at which to revisit the logic underlying this classification that possibly contains certain redundancies and omissions.

Sensitivity analysis of the 1990 duration estimates revealed that total injury YLD are largely insensitive to the assumptions regarding short-term injuries. Thus efforts should be directed towards improving the empirical basis for the long-term assumptions.

Table 2 provides some additional notes on the injury cause category case definitions. These should be read in conjunction with the ICD-10 definitions provided in Chapter 13, Table 1. The case definition for an injury is one that leads immediately to death, or that is non-fatal but severe enough to warrant hospital in patient or emergency room treatment, irrespective of whether or not an appropriate medical facility is available. Table 3 summarizes the nature-of-injury sequela case definitions used in the GDB 2001 and 2002 and their corresponding ICD codes (1).

TABLE 2 GBD INJURY CAUSE CATEGORIES AND CASE DEFINITIONS

Injuries – External Cause (refer to Chapter 14 for ICD-9 and ICD-10 definitions)	
A1. Road traffic accidents	Includes crashes and pedestrian injuries due to motor vehicles and other forms of road transportation including bicycles and animal-drawn transport.
A2. Poisonings	Only one outcome is included for poisonings.
A3. Falls	Includes falls resulting from osteoporotic fractures.
A4. Fires	Most of the sequelae of fires are due to burns. Some individuals, however, jump from buildings or are otherwise injured due to fires.
A5. Drownings	Other than drowning and near-drowning rates, the only other major disabling sequelae from near-drowning included is quadriplegia.
A6. Other unintentional injuries	This is not a residual category, but includes injuries due to environmental factors, machinery and electrical equipment, cutting and piercing implements, and various other external causes of unintentional injury.
B1. Self-inflicted injuries	Suicide attempts, whether or not resulting in death
B2. Interpersonal violence	Injuries resulting directly from exposure to interpersonal violence of a physical and sexual nature including family violence and community violence among unrelated individuals, sexual assault /rape and homicides
B3. Collective violence	Injuries directly attributable to war or organized civil conflict in combatants and non-combatants. For example, the estimates of mortality include deaths of children and adults from landmines.

TABLE 3 GBD INJURY SEQUELAE DEFINITIONS

Injuries - Type of Injury Sequelae	Injury severe enough to warrant medical attention or that leads immediately to death. In other words, injuries that are severe enough that if an individual had access to a medical facility he or she would seek care.	
	<i>ICD-9 Code</i>	<i>ICD-10 Code</i>
1. Fractures		
Skull—short-term ¹	800 to 801	S02.0/1/7/9, T90.2
Skull—long-term ¹	800 to 801	S02.0/1/7/9, T90.2
Face bones ¹	802	S02.2/6/8
Vertebral column	805	S12, S22.0/1, S32.0/7, T91.1
Rib or sternum ²	807	S22.2-9
Pelvis ²	808	S32.1-5/8, T91.2

GBD 2005 STUDY OPERATIONS MANUAL – FINAL JANUARY 2009

Clavicle, scapula or humerus ³	810-812	S42, S49.7
Radius or ulna ³	813	S52, S59.7, T10, T92.1
Hand bones ³	814-817	S62, S69.7, T92.2
Femur—short-term ⁴	820-821	S72, S79.7
Femur—long-term ⁴	820-821	S72, S79.7
Patella, tibia or fibula ⁴	822-823	S82.0-4, S82.7/9, S89.7, T12
Ankle ⁴	824	S82.5-6/8
Foot bones ⁴	825-826	S92, S99.7
2. Injured spinal cord	806 and 952	S14, S24, S34, T06.0/1, T08, T91.3
3. Dislocations		
Shoulder, elbow or hip	831, 832, 835	S43, S73
Other dislocation	830, 833-834, 836-839	S03.0-3, S13, S23, S33, S53, S63.0/1, S83.1-3, S93.1-3, T03, T11.2, T13.2, T14.3, T92.3, T93.3
4. Sprains	840-848	S03.4/5, S16, S29.0, S39.0, S46, S56, S63.5-7, S66, S76, S83.4/7, S86, S93.4/6, S96, T06.4, T11.5, T13.5, T14.6, T92.5, T93.5
5. Intracranial injuries		
Short-term	850-854	S06, T90.5
Long-term	850-854	S06, T90.5
	860-869	S25-S27, S35-S37, S39.6, T06.4, T91.4/5
6. Internal injuries		
7. Open wound	870, 872-884, 890-894	S01, S08, S11, S15, S21, S31, S41, S45, S51, S55, S61, S65, S71, S75, S81, S85, S91, S95, T01, T11.1/4, T13.5, T14.6, T90.1, T92.5, T93.5
8. Injury to eyes		
Short-term	871, 950	S05, T90.4
Long-term	871, 950	S05, T90.4
9. Amputations		
Thumb	885	S68.0
Finger	886	S68.1/2
Arm	887	S48, S58, S68.3-9, T05.0/2, T11.6
Toe ⁵	895	S98.1/2
Foot ⁵	896, 897.0-1	S98.0/3/4, T05.3
Leg ⁵	897.2-3	S78, S88, T05.4/6, T13.6

10. Crushing	925-929	S07, S17, S28, S38, S47, S57, S67, S77, S87, S97, T04, T14.7, T92.6, T93.6
11. Burns		
Less than 20%—short-term ⁶	940-947, 948.0-1	T31.0/1
Less than 20%—long-term ⁶	940-947, 948.0-1	T31.0/1
20 to 60%—short-term ⁶	948.2-5	T331.2/5
20 to 60%—long-term ⁶	948.2-5	T331.2/5
Greater than 60%—short-term ⁶	948.6-9	T31.6/9
Greater than 60%—long-term ⁶	948.6-9	T31.6/9
12. Injured nerves		
Short-term	951, 953-957	S04, S44, S54, S64, S74, S84, S94, T06.2, T11.3, T13.3, T14.4
Long-term	951, 953-957	S04, S44, S54, S64, S74, S84, S94, T06.2, T11.3, T13.3, T14.4
13. Poisoning	960-979, 980-989	T36-T65, T96-T97

NOTES

- 1 The N-codes (type of injury code) 803 and 804 were assigned to fractured skull following the distribution of N-codes 801 and 802.
- 2 The N-code 809 was assigned to fractured rib, sternum, and pelvis following the distribution of N-codes 807 and 808.
- 3 The N-codes 818 and 819 were assigned to fractured clavicle, scapula, humerus, radius, ulna and hand bones following the distribution of N-codes 810-817.
- 4 The N-codes 827 and 828 were assigned to fractured patella, tibia, fibula, ankle and foot bones following the distribution of N-codes 822-826.
- 5 The N-codes 897.4 to 897.7 were assigned to amputated toe, foot and leg following the distribution of N-codes 895, 896 and 897.0-897.3.
- 6 The N-code 949 was assigned to burns following the N-codes 940-948. In ICD-10, burns are classified by site (T20–T30) and/or proportion of body surface affected (T31). If there is no information given on the proportion of body surface affected, a decision will have to be made on how to map the T20–T30 codes across.

PROCESS FOR PROPOSING AND REVISING DISEASE SEQUELAE

The sequelae lists and definitions shown above are provisional lists based on previous GBD analyses. If the Expert Groups would like to propose revisions or additions to these lists, such proposals will be reviewed and endorsed by the Core Team to ensure

consistency with the GBD principles, as well as consistency of treatment of impairments across diseases and with the disability weights estimation. A proposal for defining or redefining disease sequelae should include the following elements:

- proposed case definitions for the disease and for the sequelae;
- a disease model summarizing the relationship between the disease sequelae and the transition rates that will be estimated;
- a brief outline of the strategy for estimating the required transition rates from the available data;
- to the extent possible, a brief description of health states associated with each sequela (following the standardized checklist approach described in more detail in Chapter 15).

Proposed revisions must adhere to the GBD principles outlined above and should also consider that a revision to the sequela list implies that incidence and other inputs for YLD calculation will need to be estimated by the Expert Group for that sequela for both sexes and all age groups in all regions.

REFERENCES

- (1) Mathers CD, Lopez AD, Murray CJL. The burden of disease and mortality by condition: data, methods and results for 2001. In: Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL, eds. *Global burden of disease and risk factors*. New York, Oxford University Press and the World Bank, 2006:45-240.
- (2) Murray CJL, Lopez AD. *Global health statistics: a compendium of incidence, prevalence and mortality estimates for over 200 conditions*. Cambridge, Harvard University Press on behalf of the World Health Organization and the World Bank, 1996.
- (3) Begg S, Tomijima N. Global burden of injury in the year 2000: an overview of methods. GPE Working Paper. Geneva, World Health Organization, 2000. URL: http://www.who.int/healthinfo/statistics/bod_injuries.pdf

CHAPTER 15

DISABILITY WEIGHTS

Disability weights are an essential data input into computations of disability-adjusted life years. These weights represent cardinal measures of health decrements on a scale ranging from 0 (signifying states that are equivalent to ideal health) to 1 (signifying states that are equivalent to being dead). This chapter presents a guide to the comprehensive revision of all disability weights for the GBD 2005 Study. First, we clarify important definitions and measurement requirements. Next, we review the procedure used to compute disability weights in the GBD 1990 Study and subsequent revisions to date. We then outline the steps that will be undertaken for estimation of the GBD 2005 Study disability weights. Finally, we summarize the key inputs that will be elicited from the GBD Expert Groups for this component of the project. Most of the material in this chapter is provided as background for those who are interested in the conceptual underpinnings and the historical evolution of disability weight measurement. Those wishing only to find the specific operational guidance for the Expert Group members may proceed to the box at the end of this chapter.

DEFINITIONS AND MEASUREMENT REQUIREMENTS

It is useful to begin with a clear enunciation of the measurement construct that the disability weights are intended to capture. Based on recent efforts to clarify the overall construct that defines burden of disease, disability weights are defined as measures of overall levels of health associated with health states rather than as measures of the utility associated with these states, or the contribution of health to overall welfare. Specifically, disability weights quantify departures from ideal health on a ratio scale (i.e. a scale that has equidistant units and a meaningful zero point). The definition of disability weights in this way has important implications for the choice of measurement approach.

For the GBD 2005 Study, disability weights are needed for every included sequela. As described in Chapters 12 and 14, for parsimony, burden of disease calculations require that the array of health consequences of different disease and injury causes be approximated with a small number of discrete entities characterized under the umbrella term of *sequela*. For most sequelae, a single disability weight is applied to time spent in that sequela under the simplifying assumption of an approximately constant, homogeneous health experience for those living in the sequela over the specified, average duration of the sequela. For a small number of sequelae, a further partitioning of the sequela may be needed to accommodate epidemiologic information on severity distribution that is not reflected in the enumeration of sequelae for that disease or injury cause, or where treatment may produce significant and specific changes in functional health. In our guidance to the Expert Groups at the end of this chapter, we elaborate on

examples where further partitioning of specific sequelae may be indicated, as this is one of the critical tasks requested of each Expert Group. As noted in Chapter 12, the disability weight for a given sequela is defined to capture the total health loss associated with time lived in that sequela, in the absence of other comorbidities. For combinations of sequelae that are likely to be highly prevalent, we will include these combinations of sequelae amongst the list of entities for which disability weights are measured, in order to adjust appropriately for any non-additive effects.

PREVIOUS PROCEDURES FOR ESTIMATION OF DISABILITY WEIGHTS

Our proposed approach for the GBD 2005 Study diverges from those used previously, so we begin by reviewing the methods used in prior efforts. Assignment of disability weights to the range of sequelae in the first iteration of the GBD 1990 study was based on first defining six different disability classes, and then mapping from each sequela into the class or classes that applied to incident cases of that sequela. The six disability classes were defined in reference to limitations in activities of daily living such as eating and personal hygiene; instrumental activities of daily living such as meal preparation; and four other domains (procreation, occupation, education and recreation). Weights were assigned to the different classes by a panel of public health experts using a rating scale approach. Once the weights associated with the six classes were determined (by averaging the values from the expert panel), the disability weight for a particular sequela was estimated by distributing incident cases across the different classes—reflecting either the proportion of time an average incident case would spend in different disability classes, or the proportion of incident cases that would be characterized by different severity levels—and computing the average weight.

For the revision of the GBD 1990 study published in 1996, a new approach to estimating disability weights was devised based on the person trade-off method. The revision of the approach was inspired by some specific criticisms of the GBD 1990 Study's approach: 1) that the disability classes were appropriate only for adults (since, for example, children were naturally dependent on adults for various of the referenced activities); 2) that no formal, replicable protocol was available to guide those aspiring to undertake a national burden of disease exercise; 3) that the class with the lowest level of disability was valued at 0.096 (on a scale on which 0 represents no disability and 1 represents disability equivalent to being dead), which produced a scale that was too blunt to capture very mild conditions; and finally, 4) that the valuation task itself did not allow the expert panelists to reflect on the policy implications of their values. New disability weights were elicited from a panel of health professionals following an explicit protocol. In the protocol a series of 22 indicator conditions were evaluated through an intensive group exercise involving two variants of the person trade-off and incorporating a deliberative process to encourage reflection on the values that emerged during the exercise. Participants were required to resolve inconsistencies in the numerical weights implied by the two alternative framings of the person trade-off. The final consistent values implied by the

reconciled person trade-off responses, averaged across participants, defined the disability weights for the 22 indicator conditions, which were then clustered into 7 different severity classes. Because each class contained several of the indicator conditions, these indicators thereby supplied an intuitive and easy-to-convey operational definition of the severity of each class.

To generate disability weights for the remainder of the approximately 500 disabling sequelae in the GBD 2005 Study, participants were asked to estimate distributions across the 7 classes for each sequela. In this second stage, the indicator conditions in each class were used as “pegs” on the scale from perfect health to near death to guide estimation of the distribution across the seven classes of disability. As described above for the first iteration, the distributions across classes were intended to reflect either the proportion of time a typical case for a given sequela would spend in each class, or the percentage of cases that would be categorized in each of the different classes. Distributions across disability classes were estimated separately for treated and untreated cases where relevant, and weights could also vary by age group.

The disability weights used for the GBD 2000-2002 updates were still largely based on the GBD 1990 Study disability weights and are summarized in Annex Tables A-6 and A-7 of Mathers et al (1). For certain conditions, where weights were not available from the GBD 1990 Study, provisional weights were used from the Dutch disability study (2) or from the Australian Burden of Disease study (3). The Dutch disability weights study used a similar protocol to the GBD 1990 Study, with the addition of health state distributions for sequelae described in terms of the EQ-5D instrument.

STEPS IN ESTIMATION OF DISABILITY WEIGHTS IN THE GBD 2005 STUDY

Several important criticisms have been raised against the approach to estimating disability weights in the GBD 1990 Study. First, the reliance on an expert panel rather than community samples has been challenged. Second, some critics have opposed to the use of the person trade-off technique for eliciting cardinal values of health states. Third, the approach to supplementing or amending the 1996 weights has been *ad hoc* rather than guided by some standardized protocol.

Our present efforts aim to respond to these criticisms and provide a transparent, rigorous and standardized approach to estimation of disability weights for all sequelae in the GBD 2005 Study, in a way that will accommodate comparable revisions in the future. Three major data collection activities are proposed, each with an associated set of data analyses:

- Community assessment of selected sequelae using discrete choice methods.
- Assessment by health professionals of all sequelae using ranking and visual analog scale methods.
- Multimethod study among highly educated respondents.

The first requirement for these efforts is a final list of sequelae, including further partitioning of selected sequelae as needed to capture important variation in severity in general, or in relation to treatment status. The final sequelae list will be determined iteratively by the Expert Groups and the core Disability Weights Sub-team, as described in Chapter 14.

In addition to the basic enumeration of sequelae, disease experts will be asked to provide standardized definitions for all sequelae following a checklist-style format to be supplied by the Disability Weights Sub-team. The checklist consists of concrete items relating to multiple health domains and symptoms that experts are asked to report on for the typical case of the given health state. The checklist is will be circulated shortly and included as an appendix to this chapter.

For the community survey, a subset of around 50 sequelae will be identified following a series of pretest investigations of a candidate list of around 100 sequelae. The selection of the candidate sequelae will be based on the following criteria:

- Health states should be familiar to most members of the lay public or possible to communicate to them with a brief definition.
- Health states should be chronic rather than acute or episodic to avoid conflation of duration with severity in the assessment exercise.

Sequelae will be presented to respondents using brief word definitions for administration in the community valuation study. These will be developed by the Core Team based on the standardized checklists provided by the Expert Groups. Pretesting of the 100 candidate sequelae, including cognitive interviews, will be undertaken in three international sites amongst convenience samples, and the pooled results will be used to guide the final selection of health states. The survey design will consist of a series of discrete choice questions in which respondents are asked to indicate which of a pair of health states they would regard as a *worse* state of health. The question must be framed to abstract away from differences in prognosis or duration to the extent possible. The survey will be undertaken among random samples in study sites located in the Philippines, Tanzania and India. Standard econometric models for discrete choice data will be used to translate the responses on paired comparisons to cardinal values for each of the sequelae.

The second set of data collection and analytic activities will have health professionals as respondents in the same study sites, with a similar approach to the one used in the community survey. The health professionals will be purposively sampled and will be administered face-to-face interviews using ranking and visual analog scale techniques. For this component, each respondent will consider subsets from the full list of sequelae, selected so that full coverage of the universe of sequelae is attained in the pooled sample. For this exercise, we will present scales with average values from the community samples as anchors for the valuation of the remaining states.

The third set of measurement activities is designed to ensure the validity of the ratio scale, especially for sequelae at the mild end of the severity spectrum. Validity and precision are particularly important for conditions with disability weights close to zero but moderate or high prevalence, since, for example, the twofold difference between a disability weight of 0.01 or 0.02 translates directly into a twofold difference in YLD, whereas many measurement methods may be too blunt to distinguish differences of these magnitudes with any confidence. We therefore propose a multimethod measurement exercise, among purposive samples of highly educated respondents in each site (e.g. university graduates), with the aim of providing an empirical basis for adjustment of the scale of estimates from discrete choice modeling and visual analog scale values in the first two sets of activities, as needed. The adjustment should be designed to yield an appropriate ratio scale for assessments of health severity. We will include measurement using standard techniques such as standard gamble and time trade-off, as well as alternative framing of these elicitation questions to bring them more clearly in line with our health measurement construct, as defined above.

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EXPERT GROUP RESPONSIBILITIES

The main inputs that will be requested from the Expert Groups in relation to this disability weights measurement will be:

1. the final list of sequelae, partitioned as appropriate to reflect important sources of variability in severity within a particular sequela; and
2. standardized descriptions of each sequela to inform the design of descriptive stimuli to be applied in the disability weights surveys.

On the first point, the Expert Groups should consider whether certain sequelae require further partitioning for the purpose of eliciting a more detailed set of relevant disability weights. Partitioning of sequelae may specify treatment status to capture relevant differences in functional health resulting from intervention; or may distinguish a small number of discrete severity levels where these distinctions are not adequately captured already in the sequelae list itself. An example of the latter includes the case of hearing impairment, for which the sequelae list may not distinguish different measured hearing thresholds but prevalence surveys may include this level of detail on the distribution of severity. In this case, separate disability weights will need to be estimated for the different severity classes and then re-aggregated to an average disability weight based on the measured distribution. For most sequelae, separate disability weights need not be attached to different treatment paths if treatment primarily affects prognosis or duration (through remission or case fatality), or the distribution of individuals across sequelae already defined in the list. An example of where it might be convenient to partition a sequela by treatment status would be chemotherapy for some cancers, where the treatment itself has side effects that are an important component of the experience of functional health for those treated.

On the second input from the Expert Groups, we note that these standardized descriptions are in addition to the case definitions described in Chapter 14, and will entail the completion of a checklist for levels of functioning on different health domains, and the presence or absence of specific symptoms associated with the typical individual living with a particular sequela. The checklist will follow as an appendix to this chapter.

CHAPTER 16

YEARS LIVED WITH DISABILITY (YLD) ESTIMATION FOR DISEASES AND INJURIES

INTRODUCTION

The fundamental objective of the GBD 2005 Study is to make valid, unbiased, comparable estimates of the incidence and prevalence of disease and injury cases or episodes and relevant disabling sequelae at the population level (for the GBD regions). These are used, together with information on duration, the distribution by severity and corresponding disability weights, to estimate the Years Lived with Disability (YLD) estimates by age and sex for all 21 regions of the world for 1990 and 2005.

YLD

There are two ways of calculating YLD. The most commonly presented are incident YLD, calculated as the stream of healthy life lost in cases of a disease or a sequela that are incident in the year of interest. The basic computation of incident YLD is incidence times average duration times disability weight. Incident YLD are added to Years of Life Lost (YLL) to calculate DALYs. Separately, prevalent YLD can be calculated as prevalence multiplied by disability weight. Incident YLD are a more “forward” looking estimate of disability in a population; prevalent YLD reflect the current disability in the population. Without discounting or age weighting, incident and prevalent YLD for a disease should be equal if there have been no past trends in incidence, mortality or remission (“cure rate”). If such trends are significant, the two types of YLD may diverge considerably. An extreme example is that in Australia there are still prevalent cases (“survivors”) of the disabling sequelae of poliomyelitis, even though there has been no incident case for many decades. The aggregate of prevalent YLD across all diseases can be used in the calculation of Health Adjusted Life Expectancy (HALE) which summarizes the mortality and disability experience of a population in a particular year.

INPUTS TO YLD CALCULATION

The data required to calculate incident YLD by age and sex include: incidence, duration and disability weight (and age at the onset of the disability if using age weights).

However, what is often available is a single measure of prevalence of the condition, limited quantitative knowledge of the natural history of the disease (e.g. duration and remission), and limited information on severity.

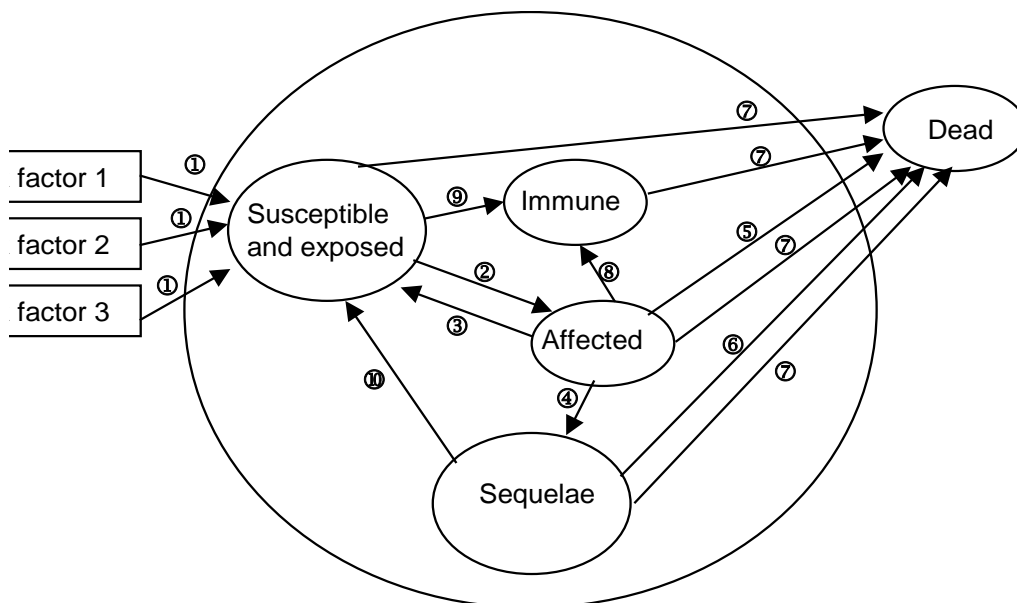
As a result, the estimation of YLD frequently depends on a wide range of different data sources specific to each disease. It requires judgment on what the most plausible source of information is and which parameters best describe the disability caused by each disease. The basis of this judgment is a good understanding of the epidemiology of the disease.

The steps involved in developing reliable and internally consistent estimates of YLD are:

1. Identify diseases and disabling sequelae, based on a review of the current knowledge of the natural history of the disease.
2. Provide a clear delineation of case definition for each of the disabling sequelae.
3. Define the epidemiological parameters needed to describe the dynamics of the disease.
 - a. When disease incidence is measured directly using high-quality and representative data, systematically review such data.
 - b. When reliable estimates of the incidence of sequela (from population data) or probability of their occurrence for each incident case (from high-quality longitudinal studies), and reliable estimates of duration of each case and each sequela (from representative population or cohort studies) are available, systematically review such data.
 - c. Since high-quality and reliable data in Steps 3 and 4 are unavailable for most diseases, decide on the most appropriate epidemiological parameters for describing disease dynamics.
4. Systematically review available data sources to estimate disease parameters.
5. Check data for consistency and quality (most likely using DISMOD; see below and Chapter 17). Note that the GBD YLD subteam will provide training and assistance for using DISMOD, and if requested by Expert Group may conduct DISMOD analysis in consultation with the expert group.
6. Submit estimates for peer review and revise estimates.
7. The final epidemiological parameters will be applied to estimate YLD as described above.

Steps 1–2 have been described and examples of disease diagrams were introduced in Chapter 14 to illustrate the choice and definitions of disease sequelae. A more generic disease diagram follows as well as more detailed descriptions of the subsequent steps.

For a good understanding of the disease it is helpful to draw a diagram of the epidemiological dynamic. This will define the epidemiological estimates that need to be developed for every component in the diagram. The following is a generic example of a disease diagram.

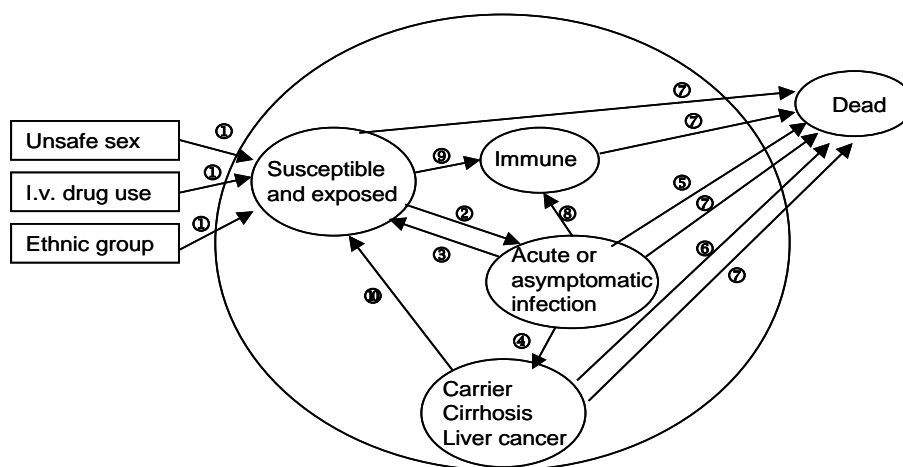


Key to the diagram:

1. Many factors can affect the exposed population. Some factors are actually diseases that increase the risk of suffering from the disease under study, e.g. diabetes and heart disease or depression and suicide.
2. Incidence of the disease: the rate at which people become newly affected by the disease under study.
3. Remission: the rate at which people with the disease stop being a case.
4. Case-complication: the rate at which patients experience a complication of the disease or start to suffer from sequelae of the disease.
5. Case-fatality: the rate at which patients die from the disease under study.
6. Complication-fatality: the rate at which patients die as a result of a complication of the disease.
7. General mortality: the rate at which the population dies from any condition other than the one under study.
8. Patients who become immune to the disease and will not be susceptible to it again.
9. People who become immunized as a result of health intervention programs.
10. People with sequelae who are exposed to the risk factor(s) and are susceptible to acquire the disease again. For instance, women who have become infertile as a sequela to gonorrhoeal infection are still susceptible to a next episode of gonorrhoea.

This diagram can become even more complex if recurrences of the clinical events associated with an intermittently relapsing disease increase the severity of the sequelae and/or the risk of dying with every new episode of the disease (i.e. rheumatic fever). Also, many diseases are interrelated and/or are risk factors for other diseases (e.g. diabetes is a risk factor for ischaemic heart disease and stroke). On the other hand, some of the parameters do not apply to certain diseases allowing a simpler disease diagram. For instance, immunity is only an issue in infectious disease and there is no remission from quite a few diseases, e.g. dementia, COPD and Parkinson. Mortality resulting from some diseases, e.g. periodontitis or osteoarthritis, is not higher than that in the general population.

Hepatitis B is an example of a disease for which most of the boxes and arrows in the generic diagram are relevant. Below is the disease diagram for hepatitis B.



Key to the diagram for hepatitis B:

1. Unsafe sex and I.V. drug use are major risk factors for infection with hepatitis B in adults. Ethnic group may be an important risk factor for the perinatal transmission of hepatitis B, as the risk of being a carrier varies significantly between ethnic groups in a population. **Estimation of at-risk groups is only relevant for disease models where incidence or prevalence is being estimated for at-risk groups using study data for those groups. If direct population-level data on incidence or prevalence are available, there is no need to include risk groups in the disease model.**
2. Incidence of the disease: the rate at which the susceptible population becomes newly infected with hepatitis B. For burden of disease estimates one would need to know what proportion of infections lead to acute illness and what proportion are asymptomatic.
3. Remission: not relevant in hepatitis B; infection leads to immunity or becoming a chronic carrier.
4. Case-complication: the rate at which patients experience complications or sequelae of hepatitis such as being a carrier, cirrhosis and liver cancer.
5. Case-fatality: the rate at which patients die from the acute infection with hepatitis B.

6. Complication-fatality: the rate at which patients die as a result of complications such as cirrhosis and liver cancer.
7. General mortality: the rate at which the population dies from any condition other than hepatitis B.
8. Patients who become immune to hepatitis B and will not be susceptible to the disease again.
9. People who become immunized as a result of health intervention programs.
10. People with sequelae who are exposed to the risk factor(s) and are susceptible to acquire the disease again. This is not relevant to hepatitis B

STEP 3: DEFINE THE EPIDEMIOLOGICAL PARAMETERS NEEDED TO DESCRIBE THE DYNAMIC OF THE DISEASE

For a disease with a single disabling health state, five epidemiological parameters describe the disease dynamic: incidence, prevalence, remission (“cure rate”), mortality (expressed as case fatality, population mortality rate or relative risk of dying) and average duration. If three of these parameters are known, the remaining parameters can be derived.

The data required to calculate incident YLD by age and sex include: incidence, duration and disability weight (and age at the onset of the disability if using age weights).

However, what is often available is a single measure of prevalence of the condition, limited knowledge of the natural history of the disease, limited information on severity and often disability weights that do not match the case definition of the epidemiological review. As a result, the estimation of YLD frequently depends on a wide range of different data sources specific to each disease. It requires judgment on what the most plausible source of information is and which parameters best describe the disability caused by each disease.

For many diseases, there may be multiple associated disabilities or a range of severity presentations. Each of these will require estimating the basic epidemiological parameters outlined above. Other diseases follow a chronic episodic course and YLD estimation will require additional data on the proportion of time spent with and without symptoms.

If a complete diagram of a disease and its disabling health states has been drawn in step 4, the most important epidemiological parameters will become apparent as all the arrows connecting disease states in the diagram need to be specified.

STEP 4: SYSTEMATICALLY REVIEW AVAILABLE DATA SOURCES TO ESTIMATE DISEASE PARAMETERS

The main task of the Expert Groups is to systematically review and/or (re)analyze published and unpublished data sources to estimate the epidemiological parameters identified for each disease and disabling sequelae. The case definitions and the disease

diagram should guide the Expert Groups on the disease parameters that have to be reviewed. It would not be possible to find all relevant studies and hence groups should follow a systematic approach to identify the best available evidence to answer the review question.

A more detailed discussion and guidelines on how to conduct a systematic review are provided in Chapter 19. There is also an example of a detailed protocol for data abstraction used by the Child Health Epidemiology Reference Group which demonstrates the scientific rigor expected of these systematic reviews.

Incidence and Prevalence

The logical starting point is a review of what is known about disease occurrence: incidence and/or prevalence. The most common parameter to describe the occurrence of infectious diseases, maternal and neonatal conditions, cancers, cardiovascular disease and injuries is incidence. The typical data sources of this parameter are disease registers, cohort studies (or in some cases serial cross-sectional representative surveys), hospital and emergency department data or disease notification systems. The occurrence of other non-communicable diseases, such as mental disorders, type 2 diabetes, osteoarthritis and dementia is typically measured as prevalence in representative national surveys or localized epidemiological studies. Recent systematic reviews of the global incidence and prevalence of schizophrenia provide a good example of what is expected in all disease areas in this study (1,2).

Remission

Remission (or the rate at which people with the disease stop having the disease, e.g. by means of a cure) is relevant for many diseases, including mental disorders and asthma, but often there may only be a limited number of cohort studies that provide evidence. A further issue is that these limited cohort studies may be reporting on remission in a selected patient population (i.e. those seeking care, or those with more severe disease), and thus may not represent the remission in the “average” case of disease in the community. Also, the definition of remission may vary between studies making it difficult to pool results. As GBD estimates reflect the health status of a population given current levels of health service, remission for some diseases can be estimated from data on access to curative interventions. For instance, cataract extraction and lens implantation surgery leads to remission from “vision loss due to cataract.”

Mortality

Mortality risk associated with the disease or disabling sequelae of interest is an essential parameter in all but a few disease models. It is important to make a distinction between deaths coded to a particular disease as the underlying cause of death in the vital registration system and the “true” excess risk of mortality in people with disease. Typically, excess mortality is quite a bit larger than the mortality coded to a disease.

Mortality and remission are the two parameters that determine the average duration of disease (one of the parameters needed to calculate incident YLD). If we would use a lower estimate of mortality by using coded deaths only, we would overestimate duration. There are multiple explanations for the higher excess mortality rate in comparison to recorded cause-specific mortality. These include coding practices or coding errors and the fact that people who die from a particular cause tend to be more exposed to risk factors (e.g. smoking, obesity or socioeconomic class) or have particular characteristics (e.g. ethnicity) that predispose to a higher risk of dying from other causes. Data on excess mortality risk typically come from a cohort study or meta-analyses of multiple cohort studies. The Asia-Pacific Cohort Study Collaboration is a good example of a systematic approach to pooling the precious data from a number of cohort studies (3). The excess mortality risk may be expressed as a relative risk or a case-fatality rate. Note that there are two ways in which relative risk measures are reported. The most common is the relative risk as a rate ratio of the mortality risk in those with disease compared to those without disease. Alternatively, it may be calculated as a Standardized Mortality Ratio (SMR), a ratio of observed deaths and “expected” deaths if total mortality rates for the population of interest would have applied. As long as the contribution of mortality from the cause of interest is small in comparison to total mortality, both measures will give similar outcomes but this may not be the case for diseases that contribute a large proportion of deaths, e.g. ischaemic heart disease deaths at the oldest ages. If the prevalence of the disease is known, the two measures of relative risk can be translated one into the other. A further example of a systematic review of the mortality risk for a disease is provided by the above-mentioned group’s work on incidence and prevalence of schizophrenia (4).

It is important to choose studies/data sources on the basis of study design quality and the relevance of the study population to the target population. Quality appraisal issues include completeness of the data; data quality; whether the data are representative of the population; and the identification of possible sources of bias. The quality appraisal issues to consider in different data sources are listed below and summarized in Table 1. In this chapter we discuss the data sources from which we tend to derive our epidemiological parameters and the data quality appraisal issues to be aware of for each type of data source. Chapter 20 describes more systematically how to address bias and missing data.

TABLE 1 DISEASE PARAMETERS AND STUDY TYPES

Parameter	Study Types	Appraisal Issues
Incidence	Cohort studies Disease registers Notification data Hospital data	Completeness Representative? Validity of case ascertainment
Prevalence	National surveys Local epidemiological studies	Representative? Validity of case ascertainment
Remission	Cohort studies of cases	Cases studied representative for all cases? Completeness
Mortality	Cohort studies	Cases studied representative for all cases? Completeness Correct ascertainment death RR vs. non-cases or total population

TYPES OF DATA, QUALITY ISSUES AND POSSIBLE SOURCES OF BIAS

DISEASE REGISTERS

Disease registers record new cases of disease based on reports by physicians and/or laboratories. Registers are common in infectious diseases (e.g. tuberculosis), cancer, congenital anomalies, a number of relatively rare diseases (e.g. cystic fibrosis or thalassaemia), and sometimes for conditions such as diabetes, schizophrenia and epilepsy. The main issues associated with these registers are the level of completeness and data quality. If a register is well kept and has good data in only part of the country, a judgment needs to be made on how representative the information is for the whole country or how the data can be adjusted to better reflect population estimates.

POPULATION SURVEYS

Interview surveys can provide self-reported information on disease conditions and impairments. Such information has severe limitations which need to be explicitly addressed before the information is used:

- There are often considerable differences between the disease concept of the “general public” and the ICD-defined disease category for which information is to be collected.

- There may be severe under-reporting of diseases for stigmatized conditions or where a significant proportion of cases are not medically diagnosed, and the respondent may be unaware of the condition, e.g. drug dependence, mental disorders, diabetes.
- Self-report may be systematically biased relative to measured data, e.g. overstating height and understating weight.
- The data may not be representative, e.g. if certain groups such as the homeless and people in institutions (e.g. prisons or old age homes) are excluded. If a disease is much more prominent in these populations (such as tuberculosis in the homeless, HIV in prisoners, and vision loss or dementia in residents of nursing homes) the overall population value of interest could be seriously underestimated. When examining survey results, the researcher has to always look at a description of the level of response and consider how selection bias could have influenced the results.

Health measurement surveys overcome some of these problems, but they still need to be evaluated for their representativeness, potential selection bias and measurement bias (validity and reliability of measurement).

EPIDEMIOLOGICAL STUDIES

If information from registers or good quality surveys is not available, epidemiological studies tend to be the next most useful source of information. If only local studies on prevalence or incidence of disease are available, the main quality appraisal issue is how representative the findings are for the larger population for which estimates are to be made. This issue inevitably requires serious consideration and depends on what is known about the variation of disease occurrence between populations and its determinants (e.g. risk factors, socioeconomic status).

Longitudinal studies of the “natural” history of a disease are a particular subset of local epidemiological studies. They can provide a wealth of information on the incidence, average duration, levels of severity, remission and case fatality. Such studies are rare because they are costly to undertake. As they are often conducted in a particular region or town, the researcher has to decide on how their results can be extrapolated to the whole population. For most diseases, so little is known about parameters such as remission, relative risk of dying and average duration that we tend to rely in our YLD calculations on the few studies carried out around the world that provide these estimates.

HEALTH FACILITY DATA

For the majority of diseases, routine data on consultations by diagnosis will not be very helpful in estimating the total burden. Facility based data — unless the coverage of the health system is nearly complete — will always be based on biased samples of the disability present in the community. Likewise, hospital deaths are unlikely to be useful due to the same problems of selection bias. Examples of conditions that can be estimated from hospital data if there is good coverage and data are available include:

perinatal and maternal conditions, meningitis, stroke, myocardial infarction, surgical conditions, and the more serious injuries. A common problem in hospital admission databases is distinguishing between episodes and people affected. If the database does not contain a unique identifier, complex probabilistic matching techniques need to be applied to determine persons who have been admitted more than once. Counting episodes of care rather than persons admitted could lead to overestimation. Another potential problem in hospital databases is that they are commonly used to determine the flow of resources from the government to hospitals. This may lead to certain diagnoses and procedure codes being favored over others if they increase a hospital's reimbursement. Comparisons over time thus become distorted and codes that would indicate more serious diseases may be overused.

The last steps in the systematic review are the summary and synthesis of relevant studies followed by an assessment of the applicability of their results. As disease rates always vary considerably with age and sex, as much detail on the age and sex distribution reported on must be retained in the summary of the studies. When presenting study results in summary tables, the Expert Groups should provide an assessment or rating of the quality of studies; and describe characteristics of the studied populations and covariates (e.g. socioeconomic status, risk factor exposure, ethnic group) that may help to extrapolate results to populations and world regions for which data are not available. At this stage it would also be useful to ensure that the reasons why other data sources were excluded are clearly documented and explained.

STEP 5: CHECK DATA FOR CONSISTENCY AND QUALITY

Very often the observed data on incidence, prevalence, and mortality cannot be simultaneously true, because they each may be measured with error, from specific subgroups of the population, or at different points in time. A major component of the work of the Expert Groups is resolving these inconsistencies and producing a consistent set of epidemiological estimates. The data source which is more likely to represent the reality in a particular community can be chosen only after serious consideration. No rules can be recommended for choosing one data source over another.

It is from this step onwards that the Expert Groups will work most closely together with the Cluster team researchers. Specifically, the GBD YLD subteam will provide training and assistance for using DISMOD, and if requested by Expert Group may conduct DISMOD analysis in consultation with the Expert Group.

Internal Consistency Check Using DisMod

Once all available data on disease parameters have been collated, the first task is to assess whether the observations are all internally consistent.

For some conditions it is possible to derive numbers of incident cases directly from disease registers, routine databases and epidemiological studies. For many other diseases

only prevalence data are available. Additionally, it is often necessary to estimate average duration from known rates of remission or death for a particular condition. DisMod is a computer software program developed for the GBD project that allows the user to check if a set of assumptions on incidence, prevalence, remission, case-fatality rates and observed mortality numbers are consistent with one another.

DisMod allows the user to change the number and size of the age groups for input and output variables as required. This is particularly useful when epidemiological parameters are listed in age groups that differ from the age groupings required to present YLD results. DisMod also allows us to supplement available data with expert knowledge, and to force the estimates to be internally consistent. The use of DisMod is described in more detail in Chapter 17.

Adjust Data for Bias and Deal with Missing Data

The estimation strategy for the YLD components is designed to produce valid estimates of the quantities of interest at the population level that are comparable across regions and over time (for 1990 and 2005 in this case). Guidelines on how to address two important issues in this process, bias and missing data, are presented in detail in Chapter 20.

Plausibility Issues

Estimates of disability incidence, duration, age of onset, and severity class must be plausible. Plausible estimates are reasonably consistent with the known epidemiology of the disease and with independent observations of the same phenomenon. For example, does the estimated average duration of the disease match what is known about the disease in the medical literature? Another example of a plausibility check is to make sure that estimates of infertility due to septic abortions, obstructed labor or sexually transmitted diseases do not exceed the total observed secondary infertility rate.

The external review component of the GBD 2005 Study work plan for estimation of YLD is an important contribution to this process of checking estimates for plausibility.

STEP 6: SUBMIT ESTIMATES FOR PEER REVIEW AND REVISE ESTIMATES

Based on the conclusions of the peer review process, the estimates of disability incidence, duration, age of onset, and severity distribution will be revised. It is important at any subsequent steps of revision to use DisMod (see Chapter 17) to re-analyze the relationships between incidence, prevalence, remission, duration, cause-specific or cause-attributable deaths and case-fatality or relative risk of death to answer the following questions:

- If data from the same source are not consistent, the question should be: how reliable is the data source?

- If DisMod produces estimates that are not consistent with the available information, does this mean that the available set of data is not consistent with the natural history model developed for this disease?
- If DisMod provides a consistent set of epidemiological estimates based on different sources right away, does this mean that the disease is so homogeneously distributed in the population and so stable and well-known as to explain this happy result, or could this be the result of chance?
- Do the numbers make sense? Are the results consistent with the published literature?

The output of this process is a consistent set of epidemiological data to calculate YLD for the burden of disease and injury.

STEP 7: APPLY DATA TO ESTIMATE YLD IN COLLABORATION WITH CLUSTER RESEARCHERS

Once all disease parameters have been estimated, reviewed and found to be internally consistent, the mechanics of estimating YLD are straightforward: for incident YLD, incident cases are multiplied by the average duration and the appropriate disability weight; prevalent YLD result from the simple multiplication of prevalent cases by the disability weight for each disabling sequela. These calculations will be done centrally by the GBD core team with the estimated YLD sent back to the Expert Group for checks and presentation in their relevant chapters and publications.

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EXPERT GROUP RESPONSIBILITIES

ESTIMATING YLD: For each of the diseases included in the GBD 2005 Study (Chapter 13) and each sequela associated with these diseases (Chapter 14) the Expert Groups should provide the epidemiological inputs for an internally consistent set of epidemiological parameters by age, sex, 21 regions, and for 1990 and 2005.

TIMELINE AND OUTPUTS FROM EXPERT GROUPS (EGS)

Phase I: March 2007 – December 2008

- Begin systematic reviews of published and available unpublished studies, surveys, and other data sources to estimate incidence, prevalence, case fatality, and mortality from each disease, and injury and prevalence and incidence from each disabling sequelae.
- Conclude first round of systematic reviews for presentation at meetings in early 2009. Systematic reviews yield estimates by age, sex, and country, and take initial steps towards regional estimates. For epidemiological parameters that can only be estimated from internal consistency analysis (for which there are no direct measurements) can be deferred until the step of regional internal consistency analysis.
- Establish definition of risk factor exposure, variable used to measure exposure in a population for each risk, and evidence on systematic bias in exposure and effect size data sources.
- Conclude the first round of systematic reviews of epidemiological studies, health surveys, health examination surveys, and other data sources to estimate risk factor exposure and effect sizes for presentation in collaborator meetings in January and February 2009.

Phase II: January 2009 – December 2009

- EG representatives who attended collaborator meetings work with rest of their group to revise estimates and look for more data based on peer-feedback.
- Internal consistency, requiring DISMOD, completed by Core Team in consultation with EGs (or by EGs if they so choose). Core Team to dialogue with EGs via e-mail and send complete sets of internally consistent estimates for External Peer Review.
- External Peer Review completed and EGs revise estimates, completing the second round of systematic reviews of incidence, prevalence, case fatality, and mortality for each disease and injury, and for risk factor exposure and effect sizes.
- EGs conclude revised round of systematic reviews of epidemiological studies, health and examination surveys, and other data sources to estimate risk factor exposure.

Phase III: January 2010 – November 2010

- Produce final internally consistent epidemiological assessments of incidence, prevalence, mortality, and disabling sequelae and final child, adult, and all cause mortality estimates arranged into league tables with data citations. Produce final estimates of age- and sex-specific exposure to risk factors for each of the designated regions, population attributable fractions, estimates of risk attributable to mortality and disability. Include analysis of trends.
- Second Consultative Meeting to facilitate coordination and finalize estimates.
- Final estimates ready for the complete GBD Study in Nov. 2010.

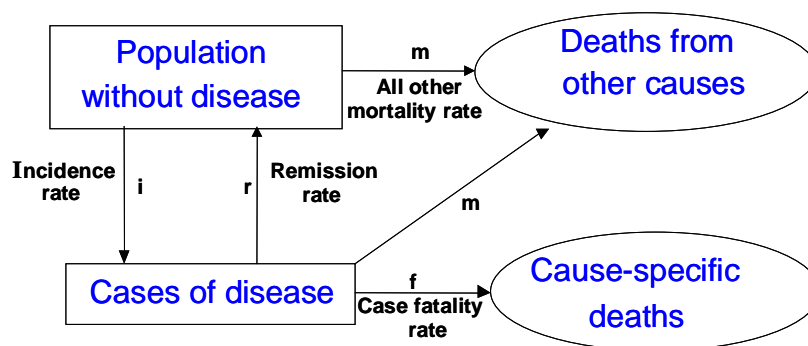
CHAPTER 17

USING DISMOD TO ESTIMATE MISSING EPIDEMIOLOGICAL PARAMETERS AND CHECK INTERNAL CONSISTENCY

INTRODUCTION

DisMod was developed for the GBD 1990 Study to help model the parameters needed for YLD calculations; to incorporate expert knowledge; and to check the consistency of different epidemiological estimates and ensure that the estimates used were internally consistent. The underlying model used by DisMod is shown below:

FIGURE 1 DISMOD DISEASE MODEL



Based on the experience with the DisMod software tool in the GBD 1990 Study, a new version, DisMod II, was developed with a number of additional features (*1*). Unlike DisMod I, which used finite difference methods to “solve” the disease model, DisMod II implements an exact solution to the underlying differential equations. In addition to calculating solutions when the three hazard rates (for incidence, remission¹, and case fatality) are provided as inputs, DisMod II allows other combinations of inputs, such as prevalence, remission, and relative risk of dying. In these cases, DisMod uses a goal-seeking algorithm to fit hazards such that the model reproduces the available input variables. DisMod II has a range of advanced features, including the ability to undertake

¹ Remission in this context describes the transition from the diseased to the “well” health state and thus is equivalent to a complete cure from the disease. This differs from the use of the word remission in some of the clinical literature where it may describe a “partial cure,” e.g. the remission of psychotic symptoms in a patient with schizophrenia without being considered cured of the disease.

sensitivity and uncertainty analyses, to give different weights to the various inputs, and to smooth inputs and specify age patterns for outputs.

DisMod II has been used in the GBD and national burden of disease studies for four main purposes:

- estimate a set of incidence rates by age from observed prevalences for a condition, given estimates of remission rates and cause-specific mortality risk derived from population data or epidemiological studies;
- check whether available data for a condition are consistent with each other, for example, when separate estimates of incidence and prevalence were available for a condition;
- calculate the average duration of incident cases, needed to calculate YLD for a condition;
- extrapolate estimates in GBD age categories from epidemiological data for different age categories.

DisMod II, however, has a number of important shortcomings. The goal seeking algorithms are very sensitive to slight changes in the age pattern of data inputs often leading to implausible age patterns of the desired output variables. While a lot more user-friendly than its predecessor DisMod I, it still requires considerable training and supervision to use competently. Another drawback is that it operates outside the main medium used in burden of disease calculations, i.e. Excel. While there are export functions to paste results into Excel, it is a cumbersome process to deal with inevitable changes in input data during the course of a study and to extrapolate one “consistent” model to a different population. Also, while there is a function to incorporate trends in the hazards of incidence, remission and/or case fatality, its implementation is rather crude (allowing only whole percentage point trends and for all ages combined). For these (and other) reasons a revision of DisMod is planned for the present GBD Study with the purpose of improving the accuracy of the goal seeking algorithms, better incorporating trends, enhancing user-friendliness and linking with methods of inferring results for world regions that have no or poor data.

The rest of this chapter provides a brief overview of the main applications of DisMod II for checking internal consistency and estimating missing epidemiological parameters, as well as instructions on how to download and install DisMod II.

A BRIEF OVERVIEW OF DISEASE MODELING

A disease process can be described by a number of variables: incidence, prevalence, remission, case fatality, duration, and mortality. These variables differ in nature. For example, incidence, remission and case fatality express transition from one state to another, while prevalence is a proportion. All these variables can, in principle, be observed, but with a varying degree of difficulty. Mortality, for example, can be relatively easily observed, but, depending on the disease, can be misclassified.

Nevertheless, many countries have cause of death statistics, which usually constitute the most reliable source of disease data.

Observing prevalence and incidence is usually much harder than mortality. Data collection, when conducted, is often limited in time and geographical area. Problems of case definition abound. Not surprisingly, data are frequently incomplete, and when available, their validity may be in doubt. In particular, given the diverse nature of the disease variables and the differences in the way the data are collected, it is inevitable that the observations are internally inconsistent. For example, when more incident cases than deaths are missed, the observed incidence will be too small for the observed mortality.

To get around these problems we exploit two kinds of additional knowledge. The disease characteristics, such as remission, case fatality, and duration, may be relatively constant among countries, and known from other countries or clinical studies. Supplementing observed data with such expert knowledge may help to overcome the lack of data. In addition to expert knowledge, we use the fact that a disease process causally links the various epidemiological variables. Any prevalent case must at some earlier point have been an incident case and will go on to recovery, death from the disease, or death from other causes. A disease model that explicitly describes these causal pathways allows us to infer missing data if sufficient disease parameters are available. For example, if incidence is not known but mortality, case fatality, and remission are, then incidence can be calculated using such disease model. Moreover, the results of the disease model are internally consistent by definition.

While different assumptions regarding remission and case fatality affect the age distribution of incident cases and YLD estimates, total YLD are relatively insensitive to these assumptions if matched to a fixed prevalence distribution. This is because YLD estimates are proportional to incidence multiplied by duration, which approximates the prevalence of the condition as long as the hazards of mortality and remission are small. In other words, for most conditions, the combination of incidence, case fatality and remission rates (and thus derived durations) used in the YLD calculations makes relatively little difference to total YLD across age groups, assuming that the same prevalence figures are used as the basis. The effects of discounting complicate this, however, with low-incidence and long-duration conditions being more affected than high-incidence but short-duration conditions.

POPULATION RATES AND INSTANTANEOUS RATES

DisMod II works internally with instantaneous rates (also known as hazards) but allows the user to input and output transition rates (incidence, remission, mortality) as population rates rather than hazards. The epidemiological literature usually reports population rates (the number of events (incidence, death or cure) in a time period divided by the mid-period population) rather than instantaneous rates, and refers to various measures of rates with inconsistent terminology (rates, risks, probabilities, hazards,

forces, etc). It is thus important to understand the differences between various forms of rates, and to ensure that inputs to DisMod are correctly specified.

In epidemiology, instantaneous rates are also calculated. It can be shown that events divided by the number of “exposure-years” or “person-years of follow-up” is the same as the instantaneous rate (as long as the instantaneous rate is constant over time). Such instantaneous rates or hazards in epidemiology may also be called “forces” or “densities,” such as an “incidence density” or “force of infection.” Note that hazards, as opposed to probabilities, can be greater than 1: they range from 0 to ∞ .

Instantaneous rates can be denominated in any units such as days, months or years. An everyday analogy to this is bank interest rates. When a bank offers a compound interest rate of 5%, it is offering an instantaneous interest rate. A 5% instantaneous interest rate will give an annual yield higher than 5%.

MEASURES OF DISEASE AND DISMOD

In this section we will discuss measures of disease frequency as used in epidemiology, and point out where differences between usual epidemiological definitions and the ones used in DisMod occur.

PREVALENCE

The point prevalence is defined as: $\frac{\text{Number of cases}}{\text{Number of people in the population}}$. Both the cases and the population are measured at the same point in time, and the cases are included in the population. Prevalence is therefore a proportion (even if epidemiologists routinely speak of “prevalence rate”).

Instead of point prevalence, in some cases “period prevalence” is reported, for example 1-month or 1-year prevalence. Period prevalence is defined as: $\frac{\text{Number of people with disease during a certain period}}{\text{Total number of people in the population}}$

Period prevalence seems to be popular among epidemiologists that study episodic disease, such as depression. The idea is to boost the number of cases, and so reduce the confidence intervals of the prevalence estimate.

Period prevalence, however, has a number of distinct disadvantages:

- the prevalence depends on the duration of the disease episode;
- a person may have had more than one episode during the period;
- the cases that have died are missed, perhaps because of their disease episode;
- recall bias is possible.

This does not mean that period prevalence is useless; for example, a 1-month prevalence estimate for major depression is a very good estimator of the point prevalence.

While DisMod I supports point prevalence only as an output, DisMod II accepts it as an input as well. Neither supports period prevalence.

INCIDENCE

Incidence estimates come in three different guises: as hazard rates, population rates, and as probabilities. We will discuss them in turn.

The incidence hazard is defined as:

$$\frac{\text{Number of new cases with disease during a certain period}}{\text{Total number of person time at risk}}$$

The incidence hazard can also be called “incidence density” and “force of incidence.”

The important part of this definition is the “person-time at risk.” Persons are at risk when alive, susceptible, and not a case. While the incidence hazard is the most precise of the three different ways to estimate incidence, it is rarely available because of the detailed measurement that is required.

As an alternative the population rate is often available:

$$\frac{\text{Number of new cases with disease during a certain period}}{\text{Average number of persons in the population}}$$

The “average number of persons in the population” serves as an approximation for the person-time at risk. As discussed above, the resulting population rate is a reasonable approximation of the incidence hazard as long as the hazard and disease prevalence are not high.

Incidence probability is defined as:

$$\frac{\text{Number of new cases with disease during a certain period}}{\text{Total number of persons at risk at the start of the period}}$$

Epidemiologists often call the incidence probability “risk,” or alternatively, “cumulative incidence,” “incidence proportion,” and “attack rate.”

Incidence probability is not supported by DisMod, but one can convert an incidence probability to a population rate. This requires the assumption that the rate is constant during the time period. The equation is:

$$\text{Rate} = \frac{-\ln(1 - \text{Prob})}{t}$$

where t is the number of time units in the period. When the probability is measured over one year and an annual rate has to be calculated, t becomes 1, and can therefore be ignored.

The reverse operation, from rate to probability, also requires the assumption of a constant rate, and uses the following equation:

$$\text{Prob} = 1 - \exp(-t \text{ Rate})$$

DisMod I only supports incidence hazard rates. DisMod II supports both incidence hazard and population rates, and the user should be aware of the difference. Since the population rate assumes that everybody is at risk, while with the hazard rate only non-cases are at risk, this means that for a given number of incident cases the hazard rate is higher than the population rate, in particular when disease prevalence is high.

MORTALITY

Mortality, either disease-specific or total, can be expressed as a rate or a probability. Statistics Netherlands, for example, reports total mortality as a probability, while disease-specific mortality is reported as a population rate. It is not clear why this is the case, but one can get around the difference using the conversion equations between probability and rate above.

Mortality rate is defined as:
$$\frac{\text{Number of deaths during a certain period}}{\text{Average number of persons in the population}}$$

When reported by a national statistical bureau, the mortality rate is always a population rate because the level of the total population person-time data is never available. But, unlike with incidence, everybody alive is assumed to be at risk, and therefore the population rate is a very good approximation of the mortality hazard rate.

DisMod needs the total mortality rate as an input. DisMod I supports the disease-specific mortality rate only as an output, while DisMod II - both as an input and an output. It should be noted that DisMod produces total attributable mortality (all mortality encompassed by the RR or case fatality rate), not necessarily the “underlying cause” mortality that would be recorded in VR data.

CASE FATALITY AND REMISSION

In epidemiology “case fatality” is almost always a probability, and refers to a short period of time. For example, the case fatality of myocardial infarction is typically assessed as the probability of death in the 4-week period after the heart attack.

DisMod is very different: in it case fatality is an annual hazard rate:

$$\frac{\text{Number of disease deaths during a certain period}}{\text{Person - time with disease during the period}}$$
, where the period stands for as year.

Note that the difference with a mortality rate is that here only persons with the disease are at risk. It should also be noted that in most of the epidemiological literature case fatality refers to the probability of dying from all causes over a stated follow-up period. In DisMod, a case fatality rate refers to the excess mortality rate in prevalent cases of

disease, i.e. their mortality rate that is greater than the average ‘background’ mortality in the population.

Remission is similarly defined in DisMod: an annual hazard rate to recover from the disease, with person-time with disease in the denominator.

RELATIVE RISK

A relative risk is the ratio of two rates (“rate ratio”) or two probabilities (“risk ratio”). In epidemiology a relative risk of death for people with a disease is defined as:

$$RR = \frac{\text{Mortality of diseased}}{\text{Mortality of non - diseased}}$$

DisMod also defines a relative risk of death for people with a disease, but does it differently:

$$RR = \frac{\text{Mortality of diseased}}{\text{Mortality of total population}}$$

The reason for this is that the relative risk of death so defined in fact serves as an alternative way to describe case fatality (CFR):

$$\begin{aligned} RR &= \frac{\text{Mortality of diseased}}{\text{Mortality of total population}} \\ &= \frac{M + CFR}{M} \\ CFR &= M(RR - 1) \end{aligned}$$

Users should be aware of this difference between DisMod and common epidemiological practice.

DISEASE DURATION

An important disease variable in Burden of Disease studies is disease duration: the years of life lived with disability (YLD) are calculated by multiplying disease incidence by duration and a disability weight. DisMod therefore has disease duration as an output, and DisMod II also accepts it as in input.

There is, however, a difference between the input and output disease duration in DisMod II: output disease duration includes the mortality from all other causes, while the input disease duration does not (there is a technical reason for this, which we will not discuss here). For this reason, disease duration is only useful as an input when the duration is short (and therefore the mortality from other causes is small).

When working with disease duration, the following relationship is useful. When case fatality and remission are expressed as annual hazards, then duration in years is:

$$\text{Duration} = \frac{1}{\text{case fatality} + \text{remission}}$$

Note that this expression ignores mortality from all other causes.

DISMOD II

DisMod II implements an exact solution to the underlying differential equations. As well as calculating solutions when the three hazard rates are provided as inputs, DisMod II allows other combinations of inputs such as prevalence, remission and case fatality. In these cases, DisMod uses the “down hill simplex method” to fit hazards such that the model reproduces the available input variables. DisMod II has a range of advanced features including sensitivity analysis, uncertainty analysis, ability to give different weights to the various inputs, and ability to smooth inputs and specify age patterns for outputs. While we plan to release a new version of DisMod for the GBD 2005 Study, those who are interested in this tool prior to the new version, should consult the following sources for more detailed guidance on its use:

www.who.int/evidence/nbd and www.who.int/evidence/dismod.

REFERENCES

- (1) Barendregt J, van Oortmarssen GJ, Vos T, Murray CJL (2003). A generic model for the assessment of disease epidemiology: the computational basis of DisMod II. *Population Health Metrics*, 2003, 1:4.

INSTALLING DISMOD II

new version of DisMod is being developed. Pending its availability, the Expert Groups may wish to use DisMod II to estimate missing epidemiological parameters (e.g. incidence from prevalence studies) or to check the internal consistency of epidemiological parameters. DISMOD III will be posted to the www.globalburden.org website when it is available, and experts will be notified at that time.

INSTALLING DISMOD II ON YOUR COMPUTER

A computer running Windows 95, 98, NT 3.5 or 4, NT 2000, or Vista, with minimum 64 MB RAM, 200 MHz processor, at least 50 Mb hard disk space and MS DAO installed is needed.

1. Go to www.who.int/evidence/DisMod
2. Click on the link [Download DISMOD II software](#)
3. Save the zipped file DisMod2_setup.zip to your hard drive.
4. Unzip file and double click on SETUP.EXE to be guided through an installation process.

SETTING UP DISMOD II FOR USE WITH THE GBD 2005 STUDY

To setup a DisMod II collection containing datasets (with population numbers and all-cause mortality rates) for each of the 21 GBD Study regions:

1. Go to www.who.int/evidence/DisMod
2. Click on the link [Background mortality and population for the 21 epidemiological regions used in the GBD 2005 Study.](#)
3. Save files to a subfolder called data within your DisMod II folder (usually at C:\Program Files\DisMod II\data) on your hard drive.
4. Open DisMod II. On pull-down menus select Data/Collection/Add then specify the collection name “GBD Study.” A window opens to allow you to identify the location of the file. Select the file “GBD Study.mdb” in your DisMod II\data folder and click on “Open.”

USING DISMOD II TO ESTIMATE EPIDEMIOLOGICAL PARAMETERS

1. Open DisMod II, and on the Data menu open the “GBD Study” collection and select the GBD region (dataset) for which you wish to develop a disease model.
2. Select menu option Diseases/New and then follow the directions given above in this chapter for entering disease descriptive data and input epidemiological data.
3. Run the disease model and inspect or export the output.

CHAPTER 18

COMPARATIVE RISK ASSESSMENT AND DISEASES AS RISK FACTORS

BACKGROUND

Data on disease or injury outcomes alone, such as death or hospitalization, tend to focus on the need for palliative or curative services. Reliable and comparable analysis of risks to health, on the other hand, is essential for preventing diseases and injuries. Analysis of morbidity and mortality due to risk factors has frequently been conducted in the context of methodological traditions of individual risk factors in ways that have limited consistency and comparability across risk factors. Comparative Risk Assessment (CRA) is a systematic assessment of the expected changes in population health which would result from modifying the population distribution of exposure to a risk factor or a group of risk factors, with a central aim of analytical and methodological consistency across risk factors.

CRA analytics can be used to quantify current mortality and burden of diseases and injuries attributable to past and current exposure, or future avoidable disease and injury burden if current and future risk factor exposure were reduced. The GBD Study will focus on the first assessment, for 1990 and 2005, consistent with the analysis of disease and injury causes. The 1990-2005 disease, injury and risk factor trends can ideally be used to develop future projections of risk factor exposure and disease and injury outcome for estimating avoidable burden.

It is important to emphasize that risk assessment, as defined above, is distinct from intervention analysis, the purpose of which is to estimate the benefits of increasing the effectiveness or the coverage of an intervention or group of interventions. Therefore, the absence of a specific intervention should not be assessed as a risk factor, but rather in measurement of intervention coverage and effectiveness.

ESTIMATING MORTALITY AND BURDEN OF DISEASE ATTRIBUTABLE TO INDIVIDUAL RISK FACTORS

The estimates of deaths and burden of disease and injuries due to risk factors in the CRA project are produced using a counterfactual approach (see Chapter 13). While the policy-relevant output of risk assessment is *the number* of deaths or DALYs that are attributable to a risk factor (the so-called “absolute risk”), the effects of risk factors exposure are commonly measured on a proportional scale in epidemiological models. As a result, we

first estimate the population attributable fraction (PAF), which is the expected *proportional* reduction in mortality if risk factor exposure were reduced to an alternative (counterfactual) distribution.

ESTIMATING POPULATION ATTRIBUTABLE FRACTIONS (PAF)

The PAF can be summarized using Equations 1A and 1B for continuous and categorical exposures, respectively.

$$PAF = \frac{\int_{x=0}^m RR(x)P(x) dx - \int_{x=0}^m RR(x)P'(x) dx}{\int_{x=0}^m RR(x)P(x) dx} \tag{1A}$$

x: exposure level

P(x): actual population distribution of exposure

P'(x): counterfactual (alternative) population distribution of exposure

RR(x): relative risk of mortality at exposure level *x*

m: maximum exposure level

$$PAF = \frac{\sum_{i=1}^n P_i RR_i - \sum_{i=1}^n P'_i RR_i}{\sum_{i=1}^n P_i RR_i} \tag{1B}$$

n: number of exposure categories

P_i: proportion of population currently in the *i*th exposure category

P'_i: proportion of population in the *i*th exposure category in the counterfactual (alternative) scenario

RR_i: relative risk of disease-specific mortality for the *i*th exposure category

It is important to note that PAF is a defined metric of effect, and not a method. Epidemiological approaches and methods simply differ on the definition of the counterfactual exposure and on methods for estimating RR (see below).

Since most diseases are caused by multiple risk factors, and because some risk factors act through other, more proximal factors, population attributable fractions for multiple risk factors for the same disease can add to more than 100%, and cannot be combined by simple addition. Multi-causality also means that a range of interventions can be used for disease prevention, with the specific choice determined by factors such as cost, technology availability, infrastructure and preferences. However, this requires particular attention in communicating the results of CRA.

PAFs will be calculated by the Core Team based on the data inputs provided by the Expert Groups, and the calculated PAFs will be sent back to the Expert Groups to be checked.

DATA INPUTS FOR ESTIMATING POPULATION ATTRIBUTABLE FRACTIONS (PAF)

Inputs needed for estimating PAF form the primary empirical work of the GBD 2005 Study and its Expert Groups are as below.

Distribution of Exposure to Risk Factor

The first step in measuring exposure to the risk factor is to select an exposure metric. Important criteria for the choice of exposure metric include:

- being a meaningful indicator of hazardous effects;
- matching with the exposure metric used in epidemiological studies that quantify hazardous effects or the availability of algorithms and models to convert between exposure metrics; and
- matching with the exposure metrics used in the available exposure data as well as algorithms and models to convert between exposure metrics.

The same exposure metric should be used in all age-sex-region groups (unless when there are physiological or epidemiological reasons for using different metrics by age and sex such as that used for being under/over-weight in children versus adults). Risk factor exposure should ideally be measured:

- using a continuous variable which may be characterized by its mean and standard deviation, or
- in multiple categories when exposure is not adequately described by mean and standard deviation (e.g. a skewed distribution), or when the exposure metric used in exposure data sources or epidemiological studies of hazardous effects is not continuous and cannot be converted to a continuous metric.

Data sources used for measuring exposure should be from the relevant age, sex, and region, or be extrapolated to an age-sex-region group using appropriate models and algorithms. Exposure data sources should be population/community representative. If the data are from selected samples (e.g. urban versus rural populations), they should be used together with evidence that allows reversing the potential bias (see Chapter 19).

Exposure-Disease/Injury Association

Selection of Disease/Injury Outcomes

Choosing the list of disease and injury outcomes causally affected by each risk factor is the first step of quantifying its hazardous effects. Further, when there is evidence for, or possibility of, differential change in incidence versus case-fatality, it should be established if the effects are on disease/injury incidence, mortality, or both. Possible

disease and injury outcomes should match those in the disease and injury cause list (Chapter 13), or, when dictated by available epidemiological studies, clusters of those causes (e.g. upper aero-digestive cancers can be used for the combination of mouth, oropharynx, and oesophagus cancers). Disease and injury outcomes that are so specific that they become a subset of a GBD disease and injury cause generally cannot be included, unless accompanied by detailed evidence on what proportion of a GBD disease and injury cause is from that outcome in different age-sex-region groups. Outcomes which are too broad in scope, such as all-cause mortality, all communicable/noncommunicable diseases, all cancers, should also be avoided. The specific composition of diseases and injuries within these broad groups often varies substantially across age-sex-region groups. An implication of the heterogeneity of cause composition is that effect size cannot be generalized as it can be for specific diseases.²

Each potential disease and injury outcome must be considered systematically for causality. A plethora of approaches have been suggested in the assessment of causality, many of which still rely on the principles proposed by Bradford Hill (2) to distinguish between causal and non-causal associations. It has also been demonstrated that these are not indisputable rules for causation, and none (with the possible exception of temporality) are absolute, as emphasized by Bradford Hill himself that they should not be taken directly as a score. The CRA project acknowledges the diversity of scientific disciplines, study designs, and methods that contribute to understanding the effects of risk factors and does not intend to set its own rigid criteria for establishing causality. Rather, for each risk factor-burden relationship, there should be a systematic and documented assessment of the likelihood of causality from epidemiological studies as well as other scientific areas, including toxicology, biological/physical understanding of disease mechanisms, etc. The use of biological/physical mechanisms as evidence for causality should however go beyond “plausibility” and provide strong evidence of a causal effect (e.g. the transmission of a biological disease agent from an infected to a non-infected person through a well-defined medium such as re-used syringe).

The final tabulated GBD Study estimates will be based on those disease and injury outcomes for which there is strong evidence of causal effects. To acknowledge the evolving nature of scientific research on causal effects of risk factors, we will consider estimates for outcomes with consistent but yet-insufficient evidence to unequivocally establish causal association, as long as unbiased effect sizes can be estimated (see below). The estimates for these outcomes with some, but not strong, evidence on causal association will be presented as secondary estimates in individual risk factor chapters and material. Examples of such outcomes include a disease for which a few small epidemiological studies have established a causal effect after appropriate control for confounding, and are consistent with effects for similar risks/diseases, but one or more

² Effects on all-cause mortality can nonetheless be used to support the presence of a causal effect. This is especially relevant when there is a statistically significant effect on all-cause mortality together with a consistent effect on mortality from multiple diseases, but the epidemiological studies are not powered for detecting a statistically significant effect of each individual disease.

larger or better-designed epidemiological studies are needed. This inclusion of secondary outcomes is based on the principle that the effects of risk factors should be neither over- nor under-estimated in a CRA analysis. These estimates must be accompanied by appropriate caveats and clarifications regarding the evidence used for inclusion as primary versus secondary outcomes. The final selection of causally associated outcomes, and the strength of evidence, will be based on the internal consultative reviews of the risk factor Expert Groups and the external peer review process. The GBD Core Team will use the internal and external reviews to ensure consistency and comparability of how evidence is used across risk factors.

Quantifying Exposure-Disease/Injury Association

A quantitative estimate of the hazardous effects of each unit or category of exposure for disease and injury outcomes is needed to calculate its PAF. In most epidemiological models, it is estimated and reported as a proportional measure of risk, such as relative risk (RR) or odds ratio (OR) (note that the appropriate effect size for the calculation of PAF is the relative risk. When odds ratios are reported in epidemiological studies, and when possible, they should be converted to RR. If this conversion is not possible, an assessment should be made on how similar or different the OR and RR may be based on the expected prevalence of disease in the population). Unlike exposure, which is population-specific, this parameter describes a causal relationship that is often “biologically determined.” As a result, exposure-disease relationships are almost always from convenient cohorts/samples or meta-analyses of data from such cohorts.

There is also an increasing body of evidence that, when the metric of exposure is comparable (e.g. accounts for duration of exposure), RR is similar across populations in different world regions. In contrast, many exposure-disease relationships are age-dependent, and some differ by sex. Therefore, for most risk factors, the RR will come from systematic reviews and meta-analyses of epidemiological studies, but it should be stratified by age and when appropriate by sex where the data are sufficient. Detailed guidelines on methods for reliably measuring and characterizing such relationships are provided in general epidemiology texts. If the age groups used in the epidemiological studies are different from those in the GBD, RRs should be estimated for GBD age-groups using a reproducible and transparent method. This method should be consistent across different risk factors and should reflect the evidence from other studies for the same risk or for other risks and/or disease outcomes that allow extrapolation. Any plausible estimation method will require mean/median age of study participants and will be coordinated across risk factors by the GBD Core Team.

There are nonetheless risk factors whose relative risks vary by region, for example for the relationship between alcohol use and injuries. More generally, it may be the case that proportional risk models are not the best way to describe the hazardous effects of some risk factors, e.g. for the risk of communicable diseases as a result of injection drug use and unsafe sexual behavior or for the effects of climate change on the risk of vector-borne diseases. In such case, alternative models may be used to estimate the exposure-

disease relationship, expressed either as relative risk or directly as PAF when the model inputs also include exposure.

Systematic reviews for each risk factor should establish if the same or different relative risks apply to disease/injury incidence, mortality, or both.

If exposure to a risk factor is removed, after some time, the relative risk of the members of a “previously exposed” group may reach that of the “never exposed,” or their risk may not be completely reversible and they have a remnant relative risk (note that absolute risk of many diseases increases with age and therefore the absolute risk among the previously exposed may continue to increase; hence risk reversibility applies to relative, and not absolute, risk). In addition to estimating the relative risk associated with an exposure, the systematic reviews should document the evidence on the reversibility of relative risk (relative to those who continue to be exposed) after exposure is removed, with emphasis on the reduction in relative risk over time.

Counterfactual Distribution of Exposure to a Risk Factor by Age Group, Sex, and Region

The third input into the PAF calculation is an alternative or counterfactual exposure distribution, in relation to which disease burden is measured. Although, by definition, this component of the PAF equation is hypothetical, it should be selected to ensure consistency and comparability across risk factors. There will be two classes of counterfactual exposure distributions in the CRA component of the GBD 2005 Study.

Theoretical-Minimum-Risk Exposure Distribution

The first counterfactual exposure distribution, also used in the CRA 2000 Study (1), is the exposure distribution that will lead to the lowest conceivable disease burden (irrespective of whether currently attainable in practice), referred to as the theoretical-minimum-risk exposure distribution (TMRED). Using the TMRED as the counterfactual has the advantage of estimating potential gains in population health by risk reduction from all levels of sub-optimal exposure in a consistent way across risk factors.

Biological principles as well as considerations of equity would necessitate that, although the TMRED may depend on age and sex, it should in general be independent of geographical region or population. Exceptions to this are, however, unavoidable when a risk factor has beneficial as well as harmful effects. An example would be the case of alcohol consumption, which in limited quantities and certain patterns has beneficial effects on cardiovascular mortality, but is always harmful for other diseases such as cancers and for injuries, e.g. accidents. In this case, the composition of the causes of death as well as drinking patterns in a region may determine the TMRED. In a population where cardiovascular diseases are a dominant cause of mortality TMRED may be non-zero with moderate drinking patterns, whereas in a population with binge drinking and a large burden of injuries it would be zero.

Despite being a hypothetical scenario, the choice of TMRED should be based on empirical evidence on exposure levels that minimize risk. The TMRED will be zero for risk factors for which zero exposure can be defined and reflects minimum risk (e.g. no smoking). For some risk factors, zero exposure is an inappropriate choice either because these are physiologically impossible (e.g. systolic blood pressure) or because there are physical lower limits to exposure reduction (e.g. concentration of particles in ambient air). For these risk factors, the lowest levels observed in specific populations and epidemiological studies may be used to choose the theoretical-minimum-risk exposure distribution, or slightly lower levels if it can be argued that further exposure reduction is possible and that the benefits of exposure reduction continue to these levels. Finally, for factors with protective effects (i.e. fruit and vegetable intake and physical activity) TMRED should be based on levels in specific low-risks populations and the level to which the benefits may continue given current scientific evidence.

Marginal Shifts in Exposure Distribution

The second group of counterfactual exposure distributions in the CRA analysis in the GBD 2005 Study will be based on shifts in the current exposure distribution to estimate the effects of marginal exposure change. The marginal shifts will be based on the difference between current exposure and TMRED, and will be standardized across risk factors by the GBD Core Team.

ESTIMATING ATTRIBUTABLE MORTALITY AND BURDEN OF DISEASE

For every risk factor, PAFs for each disease/injury outcome and for each age-sex-region group will be calculated using the above data, separately for mortality (PAF_M) and incidence (PAF_I) when the effects of exposure for mortality and incidence are different. For each age-sex-region the estimates of mortality (AM_{ij}) and burden of disease (AB_{ij}) from disease j attributable to risk factor i will be obtained as below:

$$AM_{ij} = PAF_{M-ij} \times M_j \quad (2A)$$

$$A-YLL_{ij} = PAF_{M-ij} \times YLL_j \quad (2B)$$

$$A-YLD_{ij} = PAF_{I-ij} \times YLD_j \quad (2C)$$

$$AB_{ij} = A-YLL_{ij} + A-YLD_{ij} \quad (2D)$$

These calculations will be conducted by the GBD Core Team using the calculated PAF (above) and disease-specific deaths, YLL, and YLD. The outputs will be sent back to the Expert Groups to be checked and presented in the relevant publications.

REFERENCES

- (1) Ezzati M, Lopez AD, Rodgers A, Murray CJL, eds. *Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors*. Geneva, World Health Organization, 2004.
- (2) Hill, AB. *The environment and disease: Association or causation?* *Proceed Roy Soc Medicine* – London; 58:295–300, 1965.

EXPERT GROUP RESPONSIBILITIES

The epidemiological inputs from the Expert Groups include:

- Selection of appropriate exposure metric(s).
- Estimates of risk factor exposure by age, sex, and region for 1990 and 2005.
- Selection of disease and injury outcomes with causal association together with evidence for causal effects.
- Estimates of proportional effect size (relative risk, RR) for each disease and injury outcome per exposure unit or category, with adequate adjustment for potential confounding. When RR is not appropriate, other appropriate effect sizes should be developed. Effect sizes should be by GBD age category, and when relevant, by sex and region.
- Choice of theoretical-minimum-risk exposure distribution.

CHAPTER 19

SYSTEMATIC REVIEW

The goal of the systematic review process for the GBD 2005 Study is to estimate population-level morbidity and mortality for the specified diseases, injuries, and risk factors, and to estimate the biological etiology for each disease and the causal effects of risk factors. For the former, each review will generate regional-, age-, and sex-specific estimates. Although perfect data sources will not be available for every country in every region, the systematic review process will identify all available data for the generation of the best possible estimates.

In general, reviews should focus on population-level studies, or at least those without clear evidence of selection bias, and should therefore avoid clinical populations that may lead to selection bias (however, some clinical populations such as controls in a case-control study may be appropriate). Reviews will primarily include observational studies that are carefully chosen for their quality.

PRE-LITERATURE REVIEW

DOCUMENT CASE DEFINITIONS

Prior to the start of the literature review, clear definitions should be established and documented for each disease, risk, and sequelae to be reviewed. Case definitions should be based on widely accepted standard definitions in the literature and should include confirmation with laboratory or radiology diagnoses where tests are available. A case definition used for a systematic review may necessarily differ from the case definition used to process the centralized data sources, and thus documentation is critical. Risk factor reviews should define the exact meaning of the risk for the review process and for which disease(s) the risk will be measured. All sequelae should be defined according to standard definitions and classified by degree of severity and length of sequelae where applicable.

ESTABLISH AND DOCUMENT INCLUSION AND EXCLUSION CRITERIA

All inclusion and exclusion criteria should be documented prior to the start of the review. If these criteria have to be changed due to lack of sufficient data, this must also be documented. Estimates of morbidity and mortality will be calculated for 1990 and 2005, thus data from 1980 through 2007 should be included in the review process. All regions

of the world where the disease/risk is found and all populations and ages affected by the disease/risk should be included in the review. Any additional inclusion and exclusion criteria should be added as needed for each review and documented throughout the process.

DETERMINE HOW EACH DATA SOURCE WILL BE HANDLED ANALYTICALLY

Because the variation in rigor of the study design may have a direct effect on the reported indicators for each risk, disease, or sequelae, it is important to document how different data sources will be handled analytically prior to the start of the literature review process.

LITERATURE REVIEW

DATA SOURCES

All applicable data sources, both published and unpublished studies, to ascertain individual study data should be included in the review when possible. Multiple data bases should be searched to identify all possible sources including:

- PubMed, Embase and specific databases (e.g. PsychInfo for mental disorders)
- CAB abstracts (BIDS),
- WHO library (WHOLIST), and
- SIGLE (grey literature database).

Reminder: Centralized data sources such as DHS, MICS, and VR data (where applicable) will be analyzed at the central level and thus are not the responsibility of the Expert Groups.

All searched data sources should be listed in the methods section.

SEARCH TERMS

All search terms relevant to the disease, risk, or sequelae should be included in the search process and documented in the methods section of the review. Search terms should be determined prior to the start of the review and should be broad enough to identify all possible relevant data sources applicable to estimating the burden of disease.

ABSTRACTS IDENTIFIED AND DATA EXCLUSION PROCESS

The total number of identified abstracts and reviewed papers for eligibility should be documented in the form of a flow chart. This chart should detail exclusion criteria for rejected papers at each level of the review, and present the total number of papers included in the final literature review. Figure 1 is an example of a flow chart that could be used for this process.

A clearly defined sub-sample of articles (e.g. 5% to 10%) should be read by two data abstractors. The consistency of the data between the two abstractors in the sub-sample should be reported, and if the rate of inconsistency is high, then complete double entry should be considered. Each data abstractor should use a standard form tailored to the disease/intervention of interest. The data abstraction forms from each abstractor should be compared and discrepancies resolved.

DATA ABSTRACTION

The data abstraction form should collect relevant information with regard to:

1. Study design – A thorough description of the study design will determine how the data will be included in the analysis.
2. Study population and study setting – Characterize via information provided in the paper. When additional information is needed, contact the investigator to better characterize the population. For cases where information cannot be obtained from the investigator, DHS or national/regional consensus data may be used to generalize with regard to basic population characteristics.

Special attention should be paid to the age and sex of the population, although it is recognized that this is not always possible at the review stage. Because analysis by age and sex is a critical component of the review, all details of outcome variables by age should be abstracted. Age should be recorded according to the standard GBD age categories (please see Chapter 9 – Age Groups).

3. Methods used to ascertain deaths or morbidity - Methods used to identify cause of death and case definitions of all-cause mortality rates and cause-specific mortality rates, morbidity rates, case-fatality rates, protective efficacy, comorbidity estimates, and potential flaws in the study should be documented.

METHODS

All details of the methods and assumptions used to estimate the Expert Groups' final calculations for the incidence, prevalence, severity, etc., should be documented. These methods along with the Groups' final calculations will be passed on to the Core Team for final GBD calculations. These may include but are not limited to:

- geographic regions corresponding to the risk of disease or risk of mortality from disease;
- sources and dates of population estimates;
- models to estimate seasonality;
- additional variations (e.g. transmission intensity).

The data analysis should be described in such detail that given that the data will be made available in the public database, the GBD estimates could be regenerated using similar software.

There should be a clear and detailed description of how data have been extrapolated to make regional and age-specific estimates of morbidity and mortality. This is a critical step as few diseases or conditions will have representative data for all regions, by age. Instead data from a few sites or countries will be extrapolated to produce the regional estimates. This must be clearly documented in the report.

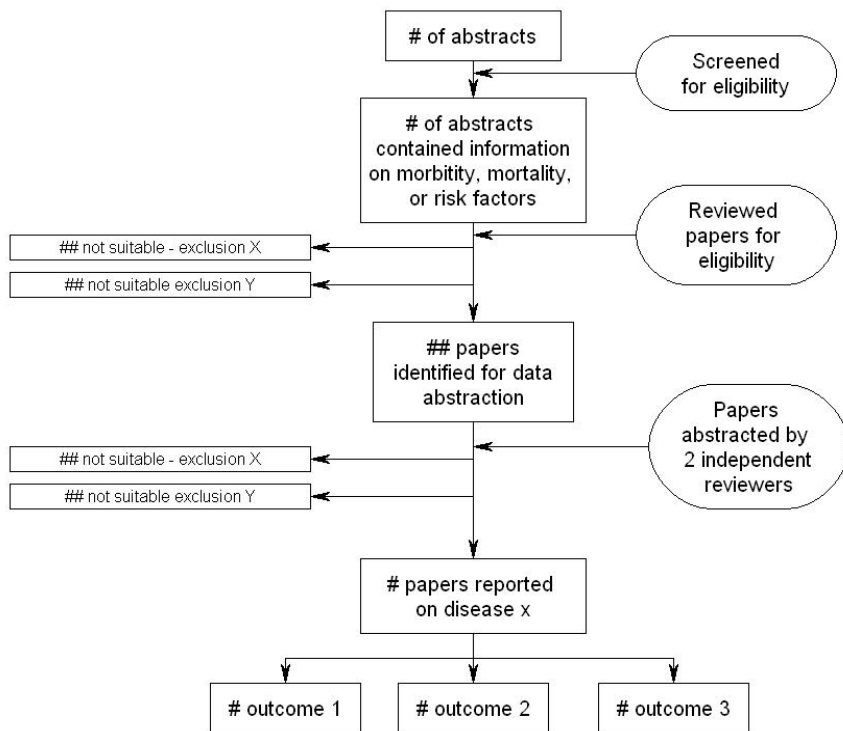
RESULTS

The detailed results of each step of the analysis should be presented in the results section. This section should include tables and subheadings summarizing the data which contributed to each step of the estimation process. Results should be broken down by age whenever possible. A flow chart should be included to pictorially illustrate how each factor of the estimating process is derived.

The calculations are meant to be transparent; thus the results section should once again include critical assumptions and an assessment of the uncertainty at each step of the estimation process. The approach used to estimate uncertainty should be clearly stated. All methods of the uncertainty analysis should be described.

Where applicable, include a sensitivity analysis with a full description of the methods and results.

FIGURE 1 SAMPLE LITERATURE REVIEW AND DATA ABSTRACTION FLOW CHART



CHAPTER 20

DEALING WITH BIAS AND MISSING DATA

INTRODUCTION

In all cases, the quantities of interest which must be estimated for the GBD 2005 Study's purposes relate to the total events or states (prevalence numbers) at the population level (national or GBD regions). The GBD Study's analytic philosophy is to:

- Use the best available data to produce estimates.
- Correct for major known biases to improve validity and cross-population comparability.
- Include a comprehensive set of disease and injury causes – required estimates are made for every cause.
- Causes where data are missing for some parameters or for some populations are estimated with wider uncertainty intervals – there are no blank cells in the output tables.
- Internal consistency is used as a tool to improve validity.
- “Prior knowledge” is used either in a Bayesian or expert sense to aid imputation to address missing data issues.

Murray has classified health statistics into three types: crude, corrected and predicted (*I*).

Crude health statistics are the measurements of indicators that come directly from primary data collection platforms with no adjustments or corrections. These figures are subject to many problems including incomplete ascertainment, non-representativeness, instrument bias, misclassification, and distortion. The only cases in which crude health statistics should be used in the GBD 2005 Study without correction relate to data that completely enumerate cases in the population without systematic measurement error (e.g. all-cause mortality for a death registration system that captures all deaths).

Corrected health statistics are measurements of indicators where two types of analytical efforts may have been undertaken: mapping to the quantity of interest and correction for a range of known biases. Mapping into the quantity of interest from an indirect correlate or consequence is based on specific assumptions and models, and introduces uncertainty due to parameter uncertainty, residual unexplained variance and model choice. Correcting for known bias ranges from routine procedures such as using sample weights in household survey analysis to more complex procedures which may involve analytical models. Correcting for known bias is extremely important if valid, reliable and comparable health statistics are to be generated; it

does, however, introduce significant scope for legitimate disagreement between analysts.

Predicted statistics are values for health statistics that are based on a model relating the quantity of interest to covariates. Two types of predicted statistics are widely used: forecasts and farcasts (where the prediction is out of sample but in the same time period). Forecasts and farcasts are often used to estimate missing data for populations. Predicted statistics have uncertainty resulting from model choice, unexplained variance in the model, and model parameter uncertainty.

The estimation strategy for the GBD 2005 Study is designed to produce valid and complete estimates of the quantities of interest at the population level that are comparable across regions and over time (for 1990 and 2005 in this case). In almost all cases, these estimates will be based on corrected statistics (corrected for known biases and adjusted to be internally consistent) and predicted statistics (forecasts from earlier studies, or farcasts from other populations) where relevant data are not available.

This chapter provides guidelines for adjusting for bias and dealing with missing data. The following sections give an overview of the main types of bias that will need to be addressed. For specific causes or types of data there may also be other important biases which the Expert Groups will have to address. The final sections of this chapter outline strategies for addressing missing data.

BIAS 1: INCONSISTENT CASE DEFINITIONS

An important first step to avoid bias is to ensure that there is a clear GBD case definition for cases/sequelae or risk factors (whose incidence or prevalence distribution is to be estimated at the whole population level by age and sex).

- Data with non-standard definitions can be used if they can be mapped to the GBD case definition (preferably using empirically observed relationships in populations).
- The same case definition **MUST** be used for estimating all the YLD inputs (incidence, duration, disability weight).
- Consistent (but not necessarily the same) case definitions must be used for YLD inputs and cause-specific mortality.
- Models or methods may be developed to map from a proxy or indirect measure of the disease/risk to the true quantity of interest, e.g. PPD surveys in children → TB incidence, Q-wave prevalence → AMI incidence.

BIAS 2: INCOMPLETENESS

The quantities of interest for the GBD 2005 Study are always events/cases/exposures in the total population (ultimately of the 21 regions). Crude data that relate to notifications, health service contacts, or diagnoses through specific sectors of the health system (e.g.

publicly funded clinics) will provide biased estimates of the quantities of interest. In some cases this may be correctable, e.g. if additional information is available on the completeness of recorded or notified cases and the potential difference in incidence or prevalence between the subpopulations captured and not captured by the data collections system.

Incomplete ascertainment or incomplete coverage is a critical problem for vital registration systems, disease registers and health service provider data. Very often it is the poor and other disadvantaged groups with the greatest health problems that do not get captured in these systems. A classic example of this problem is reported morbidity where the numbers of reportable cases of a disease are nearly always dramatic undercounts of the true number of cases occurring in the community.

“Unassigned cause” categories represent a special case of incompleteness (or misclassification bias). Where some cases are classified to an “ill-defined” or “unspecified” group, this group must be reassigned to the categories of interest, to ensure comparability of estimates across groups. For example, typically the majority of stroke deaths are classified to the ICD code for stroke unspecified. In such cases, use of the data for deaths due to ischaemic and haemorrhagic stroke without adjustment for deaths coded to the unspecified category will result in biased (and incorrect) estimates.

BIAS 3: MEASUREMENT INSTRUMENT BIAS

If there are systematic known biases in the measurement instrument, these must be quantified and the results adjusted accordingly. Thus, if a self-report instrument has a known false positive rate, this should be adjusted for. For many measurements and self-reported items on surveys, the instrument itself can be biased; self-reported weights, for example, are systematically under-reported, while self-reported heights tend to be overestimated, particularly by older people who presumably report the height of their younger adult life rather than that from a recent measurement. The prevalence of self-reported asthma based on symptom-based questions tends to be two to three times higher than if the case definition in addition stipulates a positive airway hyper-reactiveness test. The bias can also go in a different direction. The prevalence of self-reported diabetes (“Have you ever been diagnosed by a doctor or nurse with diabetes?” or “Do you suffer from diabetes?”) is typically an underestimate; even in high-income countries such as the United Kingdom or the United States, 40-50% of diabetics are undiagnosed according to health examination survey data.

For the GBD 2005 Study, special efforts should be made to establish the comparability of figures for the quantities of interest from studies in different populations and regions. This applies particularly for incidence and prevalence data, and especially for self-report data. For more biologically determined relationships, such as the duration of the average treated or untreated case or relative risks for exposure-outcome relationships, it is more

acceptable to assume that such quantities are fairly constant across populations, although it is always preferable to empirically justify such assumptions where possible.

BIAS 4: NON-REPRESENTATIVE POPULATION BIAS

For household surveys or other sampled data, non-representativeness can be a profound problem, e.g. restricted age range, one sex only, urban or rural group only, geographic, socioeconomic status or language bias. While some of these issues (missing ages, a missing sex, or missing subpopulations) may also be considered as “missing data” issues, we treat them here as “bias” issues, and restrict the consideration of missing data to situations where no relevant data are available for a national or regional population.

If the quantity of interest is known or suspected to vary across the factor on which the sample is non-representative, then the study data must be adjusted to estimate the quantity for all age-sex groups and for the whole population. This adjustment can be made using known distributions or relationships in the same country or in other countries of the region, or in some cases from an analysis of all data. For instance, if there is a systematic difference between urban and rural prevalence of diabetes, and there are some countries or regions with only urban studies: quantify the relationship and use the urban studies to estimate rural and whole population prevalence. If there is a known relationship to one or more covariates, the estimates can be adjusted to be more appropriate for the larger population. Typically, if survey data are available, covariates such as socioeconomic status, rurality, level of schooling or ethnicity may be used at the individual level. Alternatively, aggregate data at the level of subpopulations in a country or for whole countries can be used, e.g. reflecting average levels of schooling, wealth (e.g. GDP) or the proportion of the population living in cities.

Other important forms of non-representativeness may relate to the time period from which the studies are drawn. If it is known that there is a time trend in the quantity of interest, this may need to be taken into account to avoid producing a biased estimate for the target time period. If there were significant changes in effectiveness, access or availability of treatment during or after the time period of the studies, this may also need to be explicitly addressed, e.g. the scale-up of insecticide treated nets use in recent years in malaria endemic areas. Seasonality may be an issue for some causes/exposures.

BIAS 4: STUDY/PUBLICATION BIAS

An additional form of non-representativeness that cannot be as easily addressed is study population or publication selection bias based on the level of the quantity of interest. For example, validity of evidence on an important quantity of interest such as coverage with DTP3 immunization may be profoundly affected by community-level selection bias. For many diseases or risk factors, evidence may only be available from a limited number of local studies. Community studies, however, are often conducted in settings where the investigators anticipate finding larger or smaller amounts of the disease or risk factor than

expected. This is a particular problem for focal diseases such as some of the nutritional deficiencies or neglected tropical diseases. Overall, this creates a real prospect of selection bias when no national data are available. This problem is so common that efforts should be made to use more robust techniques to predict when selection bias is an issue.

BIAS 5: NON-STANDARD PREVALENCE MEASURES

The GBD Study requires estimates of average point prevalence of cases in 1990 and 2005. Point prevalence is the proportion of cases in the population at a point in time. Epidemiological studies sometimes report the so-called “12-month prevalence” or “life-time prevalence.” These are the proportions of people in the population at a point in time who were a case at any time in the preceding 12 months or their lifetime, respectively. For all except very long-duration conditions, these forms of prevalence –if measured correctly– would be significantly higher than the true point prevalence. Adjustments need to be made to such data before use. Another major problem with the use of these period prevalence estimates is that they are subject to recall bias which becomes more pronounced if the period of reporting is long.

BIAS 6: OUTLIER STUDIES

There may be a wide range of values for the measures of interest. Sometimes the disparity in the results between different studies is so large that the choice of values will result in big differences in the potential estimates. When such profound conflicts between studies/data sources arise, the recommended approach is to: 1) classify the studies on the basis of study design quality and relevance of the study population to the target population; 2) apply quality criteria to either screen out lower quality studies or to apply differential weight to them; and 3) use appropriate statistical procedures to estimate population averages from the acceptable studies.

BIAS 7: BIASES IN ESTIMATING CAUSAL EFFECTS

Analyses of causal relationships should attempt to ensure that studies take appropriate measures to control for all important confounding variables, or that the analysis makes adequate adjustments for the effects of such confounders.

When analysis of causal relationships requires the use of statistical models, models that are consistent with known measurement errors should be used. Many statistical models assume that independent variables are measured without error. The discovery that measurement error for blood pressure and serum cholesterol leads to a systematic underestimation of these hazards due to “regression dilution bias” is one graphic illustration of the problem. Unfortunately, much evidence is generated for which the potential bias introduced by measurement error in independent variables has not been adequately addressed.

MISSING DATA 1: NO DATA AVAILABLE FOR A REQUIRED EPIDEMIOLOGICAL PARAMETER

The calculation of YLD requires estimation of incidence and average duration for a case or sequela. In many cases, such information may not be measured in epidemiological studies and must be estimated using a disease model such as DisMod from other parameters, e.g. prevalence, case fatality and remission rates. The use of DisMod for this purpose is described in Chapter 17. Additionally, typical bias problems for different types of data and how to address bias through internal consistency analysis have been discussed in Chapter 17.

MISSING DATA 2: DATA MISSING FOR NATIONAL OR REGIONAL POPULATIONS

This section provides guidelines for addressing the lack of data for all countries in a region, or for an entire GBD Study region. The strategy will depend on the amount of available data (for how many populations in how many regions) and on the availability of evidence/data on predictors of variations in the quantities of interest.

While strategies for specific quantities of interest will depend on data availability, the GBD 2005 Study should attempt to ensure maximum consistency of the approach across causes and risks, and that estimation strategies are transparent and replicable. In view of these goals, the GBD Core Team plans to develop Bayesian statistical software and to make it available to the Expert Groups. In the interim, this section outlines recommendations for strategies to be used by the Expert Groups for the preparation of regional estimates. The approach depends on how many studies are available across how many populations. The GBD regions vary greatly in size.

DATA ARE AVAILABLE FOR MANY COUNTRIES IN MOST REGIONS

For example data are available for more than 50% of countries in intermediate and large regions, and at least 1 country in each of the small regions. In this case, the recommended strategy is to produce estimates for the missing countries as follows:

- Look for a quantifiable relationship with relevant covariates using regression methods. If a relevant set of covariates can be found that have statistically significant coefficients $p < .05$ and explain a substantial component of the variance, then use the regression model and predict values for missing countries. Covariates should be chosen from quantities known to be determinants or correlates for the particular quantity of interest, or general covariates such as GDP per capita, all-cause mortality levels, level of urbanization etc. For these models, using regional dummy variables may also

be appropriate as long as there is more than one observation per region. The Core Team will make available a standard dataset of general covariates.

- It may be appropriate to include in the same regression models covariates to adjust for non-representativeness, non-standard definitions, or other forms of bias.
- If there is not a lot of variance explained or suitable predictors are not known, regional averages should be calculated based on population-weighted averages for the available countries (i.e. assuming that an average based on the available countries applies to the missing countries).
- These regression models also allow for quantification of uncertainty in the predicted values by capturing ‘parameter uncertainty’, ‘fundamental uncertainty’ (the component not explained by the model), and if more than one model is used, ‘specification uncertainty’. This is discussed in more detail in Chapter 21.
- If the quantity of interest varies a lot, and this variation is thought to be real rather than due to measurement error, but there are no quantifiable covariates, analysts sometimes map the countries with missing data to the most similar countries (based on geography, epidemiology, culture, genes, etc). This strategy should generally be avoided in favor of the appropriate choice of covariates together with an estimation strategy that takes measurement error into account.

DATA ARE AVAILABLE FOR A FEW COUNTRIES IN MOST REGIONS

If for example data are available for less than 50% of countries in intermediate and large regions, the recommended strategy would be the same as in the previous case, but it may not be possible to estimate regional dummy variables because there are data for only one country in the group. If there are strong biological and other causal reasons to believe that there is a real variation in the epidemiology of the condition across regions, the residual from the regressions for a country in the region may need to be used as a crude estimate of a regional dummy variable. Uncertainty in the estimates in this case will be larger, as there will be larger parameter and specification error and most likely more fundamental uncertainty.

It must be carefully ensured that studies are of good quality and representative of the region, not giving implausible differences from other regions. One of the big problems in using such study data is that systematic but unknown bias in study or survey design can have a big influence on the results, and use of empirical data should be carefully balanced with plausibility of variation across populations.

If the few available studies are considered to be of uncertain quality or producing results that do not seem representative (even if the study design appears to be quite good), the researcher should be very cautious in relying on these studies. Instead, one should assess

the regional variations across the world, and consider whether to treat these studies as outliers and the region as having missing data completely.

IF THERE ARE NO DATA AVAILABLE FOR AN ENTIRE REGION

In this case the preferable strategy is to predict values for the region using available data for other regions, and use a model with suitable covariates.

If there is not a large amount of data elsewhere, but estimates for other regions are available, consider imputing estimates based on the regional range and a covariate, or pick a “like” region as proxy, or in the worst case situation, use the average for other (developing) or (developed) regions. Such estimation strategies will of course be associated with very large uncertainty ranges (see Chapter 21).

MISSING DATA 3: CONSISTENCY, TRANSPARENCY AND REPLICABILITY

To maximize consistency and standards for addressing the issues of bias and missing data, it is recommended that the Expert Groups draft a protocol describing their proposed approach to the preparation of regional estimates for the quantities of interest, and seek feedback from the Core Team before commencing the estimation work.

Additionally, to ensure transparency and replicability of results, the Expert Groups are requested to prepare a database of the data observations and study metadata for the studies or datasets used in producing regional estimates for the quantities of interest. The minimum contents of this database are listed at the end of Chapter 21.

REFERENCES

- (1) Murray CJL. Towards good practice for health statistics: lessons from the Millennium Development Goal health indicators. *The Lancet*, 2007, 369(9564):862-73.

EXPERT GROUP RESPONSIBILITIES

IDENTIFYING AND ADJUSTING FOR BIAS

For each of the epidemiological parameters to be estimated by the Expert Groups from data and studies, care must be taken to identify and adjust for known forms of bias. Important forms of bias that should be assessed include, but are not limited to:

1. Inconsistent case definition
2. Incompleteness
3. Measurement instrument bias
4. Non-representative population bias
5. Study/publication bias
6. Non-standard prevalence measures (e.g. 12 month prevalence)
7. Outlier studies
8. Biases in estimating causal effects (confounding, regression to mean)

ESTIMATING DATA FOR MISSING POPULATIONS (NATIONAL OR REGIONAL)

The Expert Groups should identify and implement strategies for addressing the non-availability of data for some countries in a region, or for an entire GBD region. The respective strategy should depend on the amount of data available and on the availability of evidence/data on predictors of variations in the quantities of interest, and may include a combination of simple or sophisticated statistical and causal models.

DEVELOPING A PROTOCOL FOR ADDRESSING BIAS AND MISSING DATA

Set up a database of the data observations and study metadata for the studies or datasets used in preparing regional estimates for the quantities of interest. Refer to the Box at end of Chapter 21 for further details.

CHAPTER 21

DESCRIBING AND ANALYZING UNCERTAINTY

INTRODUCTION

The GBD Study will estimate mortality and burden of disease for a comprehensive set of disease and injury causes and for all regions of the world, including regions with limited, incomplete and uncertain data. It is thus important for the project to provide some analysis and guidance on levels of uncertainty in the estimates, to allow the user of the information to assess whether the information uncertainty range is compatible with the purpose at hand. Uncertainty in the GBD regional estimates will need to be taken into account when making cross-regional comparisons, and to be carefully communicated and interpreted by epidemiologists and policy makers alike.

Uncertainty in estimates is generally difficult to quantify, since apart from the large number and disparate nature of the data sources used, there is often limited information or knowledge of the quality and potential biases in the data. The assessment of uncertainty for the epidemiological estimates will be carried out by the Core Team using the inputs provided by the Expert Groups, in order to ensure consistency. This chapter provides a brief overview of the conceptual approach to the estimation of uncertainty, and specifies the inputs needed from the Expert Groups.

Most measurement involves not only random (stochastic) error, but also systematic error, arising from biases in the measurement instrument (e.g. unrepresentativeness of a sampling frame for a survey), or from inaccuracies in the assumptions used to infer the actual quantity from the available data (e.g. estimating prevalence of a disease for a country from studies of representative subpopulations). Much of the uncertainty in estimates of population-level epidemiological parameters is associated with the assessment of systematic errors in primary data and the extrapolation from data for possibly unrepresentative subpopulations to whole populations.

Uncertainty may arise from several important sources:

- Stochastic variation (e.g. when we base estimates for a population on observations from a sample).
- Systematic (non-random) biases (e.g. how representative for the whole population are the estimates from the study of a subgroup; how validly does the survey instrument address the quantity of interest). Disagreements between sources may often be an indication of systematic bias in one or several sources.

- Use of models when there are missing data. Uncertainty from using models to estimate missing values can be divided into three components: specification uncertainty from the choice of which model to use; parameter uncertainty due to the uncertainty in the coefficients estimated for a given model, and fundamental uncertainty, the component of variation that is not explained by a given model.

GENERAL APPROACH TO THE QUANTIFICATION OF UNCERTAINTY

The general approach of the GBD 2005 Study to describing and estimating uncertainty in quantities of interest is to represent them as probability distributions using a Bayesian interpretation of probability as expressing uncertainty of an observed or hypothetical event given a set of assumptions about the world (*1*). Analytic methods for dealing with uncertainty have been facilitated enormously by the revolution in computer technology. Using such technology, the general approach to propagating uncertainty in estimates relies on numerical simulation method (*2-4*).

UNCERTAINTY IN YLD ESTIMATES

To enable the Core Team to carry out quantitative assessments of uncertainty for epidemiological estimates, the Expert Groups working on reviews and analyses for the estimation of YLD should also prepare:

- A protocol summarizing their approach to the regional estimation of the quantities of interest, including strategies for adjusting for bias and for estimating missing data. Where regression models are used, full descriptions of these should be included.
- A database of the data observations and study metadata for the studies or datasets used in preparing regional estimates for the quantities of interest. This database should contain the data points used from studies, together with information specifying the study-specific confidence intervals for these data points. The recommended contents of this database are listed in the following section.

For a given quantity of interest (e.g. incidence, prevalence, case fatality, risk exposure distribution), the Expert Groups should document the following information for every study used in the analysis.

STUDY METADATA

1. Citation – Bibliographic reference to the publication or data source specifying authors, type of publication, publication year, etc.
2. URLs should be provided for publications or datasets available on the worldwide web.

3. Study population (national, subnational or other subpopulation (describe)). Also specify subpopulation strata for which study results are available (e.g. urban/rural), particularly for population characteristics used for bias or missing data adjustment.
4. Sample size
5. Study design and setting (community cross-sectional survey, longitudinal survey, etc.)
6. Sampling strategy (simple random, cluster sampling, etc.; include design factor if relevant)
7. Time period of data collection
8. Sexes covered (male, female, or persons not further categorized by sex)
9. Age range covered
10. Case definition / measurement technique
11. Additional known biases for which adjustments were made

STUDY DATA

1. Study data by age and sex categories used for the analysis - these will normally relate to the most detailed age categories available from the study, not estimates adjusted to GBD age categories. Where study data are also available for relevant subpopulations, provide these data as well.
2. Confidence intervals for study observations, where available. If not available, the study metadata should contain sufficient information (e.g. sample size, design factor) to enable estimation of confidence intervals. Confidence intervals here refer to the study estimated confidence intervals (usually reflecting sampling issues and possibly measurement error). Non-stochastic sources of uncertainty may often be of much more importance, but will be estimated statistically from the complete set of studies.

The data analysis should be described in such detail that given the data made available in the public database, the GBD estimates could be regenerated using similar software.

METHODS

All details of the methods and assumptions used to produce the final calculations for the incidence, prevalence, severity, etc. should be documented. These methods along with the Expert Groups' final calculations will be passed on to the Core Team for final GBD calculations and uncertainty analysis.

There should be a clear and detailed description of how data have been extrapolated to make regional and age-specific estimates of morbidity and mortality. This is a critical step as few diseases or conditions will have representative data for all regions, by age. Instead data from a few sites or countries will be extrapolated to produce the regional estimates. This must be clearly documented.

Optionally, the Expert Groups may be able to provide information on uncertainty around severity distributions for sequelae health states, which will assist in the estimation of uncertainty ranges for average disability weights by the central Disability Weights Sub-team.

REFERENCES

- (1) Morgan MG, Henrion M. *Uncertainty: a guide to dealing with uncertainty in quantitative risk and policy analysis*. Cambridge, Cambridge University Press, 1990.
- (2) King G, Tomz M, Wittenberg J. Making the most of statistical analyses: improving interpretation and presentation. *American Journal of Political Science*, 2000, 44(2):341-355.
- (3) Vose D. *Risk analysis: a quantitative guide*. New York, Wiley, 2000.
- (4) Salomon JA, Mathers CD, Murray CJL, Ferguson B. *Methods for life expectancy and healthy life expectancy uncertainty analysis*. GPE Discussion Paper No. 10. Geneva, World Health Organization, 2001. URL: <http://www.who.int/healthinfo/paper10.pdf>

EXPERT GROUP RESPONSIBILITIES

PROTOCOL FOR PREPARATION OF REGIONAL ESTIMATES

After completion of estimates, prepare a detailed protocol of the methods and assumptions used to make final calculations. These methods along with the input dataset (see below) and final calculations will be passed on to the Core Team for final GBD calculations and uncertainty analysis.

DATABASE OF STUDY OBSERVATIONS AND METADATA

Prepare a database of the data observations and study metadata for the studies or datasets used in producing regional estimates for the quantities of interest. For each study include the following minimum set of information:

<i>Study data</i>	<i>Study metadata</i>
<ol style="list-style-type: none"> 1. Study data by subpopulation, age and sex categories used for analysis 2. Confidence intervals for study observations, where available. 3. If CI not available, sample size and design factor data. 	<ol style="list-style-type: none"> 1. Citation 2. Relevant URLs 3. Study population 4. Subpopulation strata for which results available 5. Sample size 6. Study design and setting 7. Sampling strategy 8. Time period of data collection 9. Sexes covered 10. Age range covered 11. Case definition / measurement technique 12. Additional known biases

CHAPTER 22

PUBLICATION AND PEER REVIEW PRINCIPLES

This section presents an overview of the principles for publication and the peer review process.

PUBLICATIONS

The work for the GBD 2005 Study will be reflected in three types of publications:

1. Journal articles and book chapters that present the following *for individual diseases and risks*:
 - epidemiological parameters such as disease- or risk factor-specific estimates of incidence, prevalence, or effect sizes;
 - the burden of disease.
2. Journal articles and book chapters that present new methodological developments or the work of cross-cutting sub-teams such as mortality, causes of death, or disability weights.
3. Journal articles, book chapters and official reports that present mortality or burden of disease estimates across multiple diseases and risks.

PUBLICATIONS ON INDIVIDUAL DISEASES AND RISKS

The GBD Study assumes that papers will be published in scientific journals reporting new estimates of incidence, prevalence or other epidemiological parameters for individual diseases, conditions or risk factors. When the Expert Groups decide that the work they are undertaking for the GBD 2005 Study is ready for scientific review and publication, they may submit it. However, such epidemiological parameters must be described as “interim” or “ongoing” (versus “final”) until the official estimates of global burden of disease for 1990 and 2005 are completed. For papers based in part or entirely on work done through the GBD 2005 Study, the authors are asked to acknowledge any financial, methodological, or logistical support received from the GBD 2005 Study as well as from other agencies and institutions. Beyond epidemiological parameters, subsequent to, or simultaneous with, the official GBD Study’s publication, the individual expert working groups are also encouraged to publish the resulting mortality and burden of disease (i.e. DALYs) estimates for their specific disease, injury or risk factor. In practice, since DALYs will be calculated only after other epidemiological parameters are finalized, this timing will coincide with the actual estimation process. Note that the decision on authorship of such materials is entirely up to the Expert Groups (including whether all or some Expert Group and Core Group members should be listed as authors based on their respective contributions).

NEW METHODS OR THE RESULTS FROM CROSS-CUTTING SUB-TEAMS

The GBD Study will undoubtedly stimulate new methodological developments that are relevant to the estimation of mortality, causes of death, disability weights, the computation of uncertainty, and potentially other areas. We expect that this work will generate scientific journal articles that will be authored by the members of the relevant Sub-teams following standard academic principles of authorship. Where these publications include results such as age-specific all-cause mortality rates, these results should be identified as interim, pending the finalization of the GBD 2005 Study in the same way that results of the Expert Groups' work on individual diseases are identified as interim.

CROSS-CUTTING PUBLICATIONS AND OFFICIAL GBD STUDY PUBLICATIONS

In addition to publications on individual diseases and methods, we anticipate several levels of publications from the GBD 2005 Study that give estimates *across diseases, injuries, and risk factors*. The GBD Study Core Team will be solely and exclusively responsible for all final estimates of deaths and DALYs included in the final GBD report. No other group can claim that its numbers for deaths and DALYs are endorsed by the GBD 2005 Study or announce final numbers until the final report is released.

When published as journal articles, these cross-cutting publications will have group authorship by the whole GBD collaborative group, implemented as common in large collaborative projects. The primary responsibility of producing these papers will be with the Core Team of the project.

In addition, there will be at least one, and perhaps multiple volumes produced as part of the GBD 2005 Study. These volumes will be edited by members of the Core Team, but individual chapters of diseases or risk factors will be written and authored by the Expert Groups as above, with a particular Group being responsible for completing a chapter on time and for the final list of authors of that chapter. Corresponding members of the Expert Groups will be acknowledged appropriately in the chapters or in one place in the edited volume.

All official GBD Study publications (i.e. official reports and edited books) will have the names of the five key institutional partners listed – Harvard University, Institute for Health Metrics and Evaluation at the University of Washington, Johns Hopkins University, University of Queensland, and the World Health Organization.

PEER REVIEW

The overall study design also includes a process of scientific peer review that will be conducted as part of the work and will take place prior to the submission of results to

peer-reviewed journals. Peer review for the GBD 2005 Study by international experts not directly involved in the analysis is essential for two purposes:

- to evaluate the validity and appropriateness of data, methods, models, and assumptions used for the estimates of epidemiological relationships and parameters, and the resulting estimated parameters themselves, related to individual diseases, injuries and risk factors; and
- to evaluate consistency of data, methods, models, and assumptions across diseases, injuries, and risk factors.

The peer review process may also help uncover unused data sources, identify simple computational and analytical mistakes, and broaden participation in the Study.

The following assessments will be made during the peer review process:

1. Have the authors used the best and most recent sources of information for estimating the epidemiological parameters of the relevant disease, injury, or risk factor (in the case of risk factors, this will also include evidence of causal effects as well as theoretical-minimum-risk exposure)?
2. Have they excluded any relevant epidemiological relationships (e.g. disease sequela or risk factor outcome) or relevant data sources? If yes, have they provided convincing arguments for doing so?
3. In estimating the relevant epidemiological parameters, have the authors adequately accounted for sources of bias and selection? Are there expectations of residual bias?
4. Is the extrapolation of epidemiological parameters to populations or age groups with limited or no direct studies based on appropriate models and assumptions?
5. Are the resulting estimates of the epidemiological parameters, their age and regional patterns, and the associated burden of disease, consistent with direct studies for this disease/injury/risk factor or in comparison with other similar or related diseases/injuries/risk factors?
6. How is the uncertainty of the assumptions, in relation to alternative possible assumptions, expected to affect the estimates of the epidemiological parameters and the resulting burden of disease/injury/risk factor?
7. Are the methods and data sources well documented and transparent?