REPORT

Epidemiological Methods in Community Genetics and the Modell Global Database of Congenital Disorders (MGDb)

Bernadette Modell MA PhD MB BChir FRCOG FRCP

Matthew W. Darlison BA MA PhD

Centre for Health Informatics & Multiprofessional Education (CHIME), University College London, London, UK.

Sowmiya Moorthie PhD MSc

PHG Foundation, Cambridge, UK.

Hannah Blencowe MB BS MSc

Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK..

Mary Petrou BSc PhD

Institute for Women's Health, University College London, London, UK.

Joy Lawn MB BS PhD

MARCH Centre, London School of Hygiene and Tropical Medicine. WHO Child Health Epidemiology Reference Group (CHERG)

On behalf of the International Collaborative Group on Global Epidemiology of Congenital Disorders.

Preface: About this Document

The Articles and Annexes contained within this document constitute the most fine-grained description of the methods and approaches devised in the course of a large collaborative exercise since the 1980s to make estimates of the epidemiology and associated health burden of congenital disorders.

The work began at a scientific meeting at WHO Headquarters in Geneva, and has continued in various forms ever since, with input from more individuals than it is possible to acknowledge via the conventional methods of shared authorship.

This document is a work in progress, and so its various portions are under development, in the course of which they have been shared with members of the international collaborative group. As the component texts reach the requisite level of maturity, will be added to this document to enable wider consultation with the global community of interested parties.

Earlier access to some or all of the texts may be possible – contact b.modell@ucl.ac.uk and m.darlison@ucl.ac.uk to discuss this.

International Collaborative Group on Global Epidemiology of Congenital Disorders

The group has been coordinated and meetings convened from London by UCL (WHO Collaborating Centre for Community Genetics) and the London School of Hygiene & Tropical Medicine (MARCH Centre).

Core Team

Bernadette Modell, emeritus professor of community genetics, Co-director and Clinical Lead, WHO Collaborating Centre for Community Genetics, Centre for Health Informatics & Multiprofessional Education (CHIME), University College London. b.modell@ucl.ac.uk

Matthew Darlison, Co-director and Informatics Lead, WHO Collaborating Centre for Community Genetics, Centre for Health Informatics & Multiprofessional Education (CHIME), University College London. m.darlison@ucl.ac.uk

Sowmiya Moorthie, PHG Foundation, Cambridge UK.

Hannah Blencowe, Research Fellow, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine.

Mary Petrou, Honorary Senior Lecturer, Institute for Women's Health, University College London. (Head, prenatal diagnosis of haemoglobin disorders).

Joy Lawn, professor of maternal reproductive and child health. Director, MARCH Centre, London School of Hygiene and Tropical Medicine, UK and Co-ordinator, Neonatal Team, WHO Child Health Epidemiology Reference Group (CHERG).

Collaborative Network

Alan Bittles, Honorary Professor of Community Genetics, School of Medical and Health Sciences, Edith Cowan University, and Adjunct Professor and Research Leader, Centre for Comparative Genomics, Murdoch University, Perth, Australia.

Arnold Christianson, Professor of Human Genetics, National Health Laboratory Service and University of the Witwatersrand, Johannesburg, South Africa.

Simon Cousens, Professor of Epidemiology and Medical Statistics, London School of Hygiene and Tropical Medicine.

Stephen Gibbons MSc, PhD, Professor of Economic Geography and Research Director, Spatial Economics Research Centre, Department of Geography and Environment, London School of Economics, UK.

Hanan Hamamy, Professor Emeritus of Human Genetics, Department of Genetic Medicine and Development, Geneva University Hospital, Switzerland.

Babak Khoshnood, Paris registry of congenital anomalies (EUROCAT contributor), Paris, France

Christopher P. Howson, latterly Vice-President for Global Programs, March of Dimes Foundation, White Plains, NY, USA.

Pierpaolo Mastroiacovo, Professor of Paediatrics, Director, Alessandra Lisi International Centre on Birth Defects and Prematurity and Pensiamoci Prima Project, Director, Centre of the International Clearinghouse for Birth Defects Surveillance (ICBDMR) and Research WHO Collaborating Centre.

Khaled Yunnis, Director National Collaborative Perinatal Neonatal Network, American University of Beirut, Lebanon.

Joan Morris, EUROCAT Director of Research, Wolfson Institute of Preventive Medicine, Barts and The London Hospital, London UK.

Peter Mossey, Professor of Craniofacial Development and Director, WHO Collaborating Centre for Craniofacial Anomalies, Dundee University Dental School, Scotland, UK.

Sue Povey, Emeritus Professor of Human Genetics, University College London, UK.

Judith Rankin, Professor of Maternal & Perinatal Epidemiology, Institute of Health & Society, Newcastle University, UK.

Lavinia Schuler-Faccini, Universidade Federal do Rio Grande, Porto Alegre, Brazil.

Christopher Wren, Consultant Paediatric Cardiologist (retired), Freeman Hospital, Newcastle upon Tyne.

Helen Malherbe. School of Clinical Medicine, University of KwaZulu-Natal, South Africa.

Ashraf Samavat, Head, Genetics Unit, Ministry of Health and Medical Education, Tehran, Iran.

Collaborative Network – Former Members

RJ Berry, Medical epidemiologist, Prevention Research Branch, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia.

Helen Dolk, Professor of Epidemiology and Health Services Research, latterly EUROCAT Project Leader, and Director, WHO Collaborating Centre for the Surveillance of Congenital Anomalies, University of Ulster, Northern Ireland, UK.

Acknowledgements

B Modell is a retired Wellcome Principal Research Fellow. This work was earlier supported by the Wellcome Trust as part of developing the science of community genetics.

UCL Centre for Health Informatics and Multiprofessional Education (CHIME) has given the work a home and generous support in kind from 1997 to the present.

This work is currently supported by the WHO Office for the Eastern Mediterranean Region.

Contents

Figures

Tables

Part I: A General Method for Establishing the Global Epidemiology of Congenital Disorders

Article 1: Introduction: scope and general overview

Abstract

Congenital disorders (birth defects), are pathological conditions arising before birth, whether evident at birth or manifesting later in life. They fall into two main groups: those with environmental causes (maternal infection or illness, or exposure to teratogens) and those with mainly endogenous causes (chromosomal disorders, single gene disorders, most congenital malformations, disorders due to genetic risk factors) here called *constitutional congenital disorders.*

Congenital disorders are important causes of early death and disability. However their contribution to the global burden of disease is seriously under-estimated because of difficulty in obtaining local observational data in many countries. The Modell Global Database of Congenital Disorders – MGDb – is an instrument designed to overcome this problem. This series of articles describes the methods used in the Database to generate the country-specific estimates for the birth prevalence and outcomes of constitutional congenital disorders published online in the appendices.

Estimates are based on the following evidence-based assumptions on baseline birth prevalence, i.e. the prevalence that would apply in the absence of any intervention. (a) Chromosomal disorders: birth prevalence of Down syndrome and other trisomies varies with maternal age while that of other disorders is relatively constant. (b) Congenital malformations: when environmentally-determined malformations are excluded, there is little evidence for country differences in birth prevalences with the exception of neural tube defects and oro-facial clefts. (c) The baseline birth prevalence of most single gene disorders is determined by a balance between new mutation and loss of harmful variants by natural selection: therefore their collective birth prevalence varies little between populations. (d) Global data is available on the prevalence of parental consanguinity, the principal factor affecting the birth prevalence of recessively-inherited disorders. (e) Some genetically determined disorders are common because the responsible gene variant also confers a selective advantage: available data on gene frequencies permits country-specific calculation of the birth prevalence of haemoglobin disorders, rhesus haemolytic disease and neonatal jaundice due to glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Once baseline birth prevalence is known, it can be combined with demographic and other data to reach country-specific estimates of annual affected births, and to quantify the effects of interventions. This approach is used in the current version of the Global Database to generate country-specific estimates for severe, early-onset constitutional congenital disorders, specifically designed to meet the information needs of policy-makers.

This introduction focuses on two main points.

- The need for an agreed terminology for use in community genetics. Lack of clear, agreed definitions causes confusion and undermines consensus. For example, the term congenital *anomalies* (which covers only chromosomal disorders and congenital malformations) is widely thought to apply for the totality of congenital *disorders*, and this contributes to the current misperception of their public health importance. As a first step towards consensus, this Introduction includes a set of proposed definitions of terms for use in Community Genetic epidemiology.
- Contrasting estimates for under-5 deaths due to congenital disorders. For congenital *anomalies* alone, the Global Burden of Disease (GBD) estimate for 2000 was 3.3 under-5 deaths /1,000 births: WHO and GBD estimates for 2010 are 2.02 and 3.7/1,000 respectively. These contrast a March of Dimes estimate of 9-10/1,000 for 2000, and Global Database estimate of 8/1,000 for 2010. The Global Database estimate for total congenital *disorders* is 15 under-5 deaths /1,000 births.

The remaining articles describe the methods used in the Global Database in sufficient detail to allow critical review and enable the interested reader to replicate and apply the method locally.

The articles, and the current Global Database, are the product of an international collaboration intended to improve the quality and availability of evidence on the birth prevalence and outcomes of congenital disorders.

1.1 Introduction

Congenital disorders (also called *birth defects*) are defined as "any potential pathological conditions arising before birth --- whether they are evident at birth or become manifest later in life" (WHO (1985a), (2000) and (2006)). They cover a wide range of severity, can affect any aspect of structure or function, and are an important cause of early death and life-long disability. They fall into five main groups (Figure 1.1).

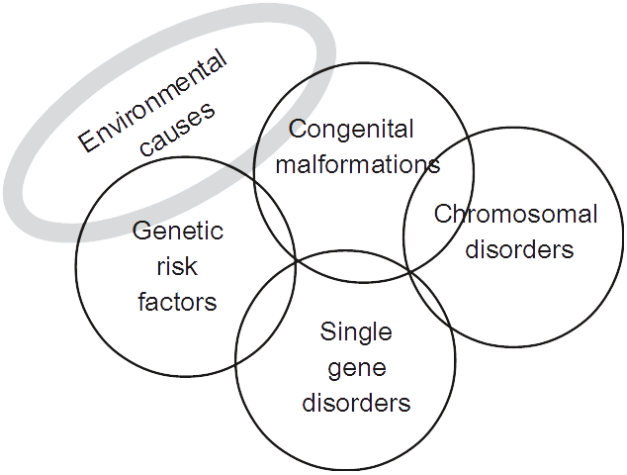

Figure 1.1. The main groups of congenital disorders. Some have known environmental causes, some have genetic causes (chromosomal disorders, single gene (Mendelian) disorders, disorders due to genetic risk factors), and some (including many congenital malformations) have no known cause and could occur in any pregnancy. However there is considerable overlap between groups. The image is notional: there is no relation between size of the circles and frequency or actual degree of overlap. (The outline of environmental causes is indicated differently because of uncertain and changing birth prevalence.)

The burden of congenital disorders can be greatly reduced by appropriate interventions. However accurate diagnosis can require specialist clinical and laboratory facilities: under-estimation is inevitable when these resources are not available. Consequently, in large parts of the world the absence of reliable epidemiological data leads to serious under-estimation of the public health importance of congenital disorders, and impedes policy development.

We propose that this problem can, in large part, be overcome because four major groups - chromosomal disorders, congenital malformations, single gene disorders, and disorders due to common genetic risk factors - have (mainly) endogenous causes. Consequently their birth prevalence[1] in the absence of any intervention (their *baseline birth prevalence*) is relatively stable in any given population, and is largely independent of environmental change. In practice sufficient observational data exists to support evidence-based estimates of the baseline birth prevalence of these congenital disorders for any country. This (possibly) unique characteristic offers an extraordinary advantage to the epidemiologist, because it provides a relatively stable baseline against which to assess all estimates of outcomes and effects of interventions.

[1] Throughout this series the term "birth prevalence" is used instead of "incidence" to describe the frequency of new cases as they present to health services (see definitions in terminology section below).

Furthermore, outcomes in the absence of intervention and with available interventions are known for most groups of congenital disorder.

It is possible, in principle, to relate these rates to demographic and other available data, and so reach evidence-based, country-specific estimates of actual affected births, and to quantify the effects of interventions, for almost any country.

In view of this important common characteristic, these groups are here collectively called *constitutional congenital disorders*.

We have tested the above proposal by creating a system that generates country-specific epidemiological estimates of severe[2], early-onset[3] constitutional congenital disorders specifically designed to meet the information needs of policy-makers – the Modell Global Database of Constitutional Congenital Disorders (MGDb or "the Global Database" for short). This series of articles aims to describe the methods used in sufficient detail to enable criticism, improvement, and their wider application.

Background of the Global Database

The need for epidemiological data on congenital disorders was recognised in the 1950s, partly in order to be able to assess effects of exposure to atomic radiation. This led on to development of some population-specific registries (e.g. the British Columbia Health Surveillance Registry in 1952 (Baird 1987) and the Hungarian Congenital Abnormality Registry in 1962 (Czeizel 1997)), and some large-scale surveys in the USA (e.g. Trimble and Doughty (1974), Myrianthopoulos and Chung (1974)). The observations on congenital anomalies were broadly consistent (Czeizel and Sankaranarayanan 1984) and were thought to apply generally for populations of Northern European origin. A WHO comparative study of the birth prevalence of selected congenital malformations in 24 centres representing all WHO regions again gave broadly consistent results (Stevenson, Johnston *et al.* 1966).

In the 1980s the WHO Hereditary Diseases programme continued to develop the global picture, starting with the global epidemiology of haemoglobin disorders (Gross 1983) and preliminary estimates for the full range of congenital disorders (WHO 1985a). The initiative was continued by the WHO European and Eastern Mediterranean Regional offices (Modell, Kuliev *et al.* (1991), Alwan, Modell *et al.* (1997)[4]. It provided a quantitative basis for the March of Dimes Global Report on Birth Defects (Christianson, Howson *et al.* 2006), which in turn led to inclusion of congenital disorders in the Global Burden of Disease study, and development of the Born Healthy needs assessment toolkit (Nacul, Stewart *et al.* (2014) and www.bornhealthy.org). These in turn prompted development of the database to cover outcomes as well as birth prevalences, and to ensure rigorous review by international experts.

[2] That cause early death or disability in the absence of intervention.
[3] That present before 20 years of age.
[4] The WHO initiative began with creation of a database of haemoglobin disorders (see Modell, B. and M. Darlison (2008). "Global epidemiology of haemoglobin disorders and derived service indicators." Bull World Health Organ **86**(6): 480-487. and www.modell-almanac.net), was progressively extended to include other disorder groups, and provided input for several reports (WHO (1985a). Community approaches to the control of hereditary diseases. Report of a WHO Advisory Group on Hereditary Diseases. Geneva 3-5 October 1985. Unpublished WHO document., WHO (2000). Primary health care approaches for prevention and control of congenital and genetic disorders : report of a WHO meeting, Cairo, Egypt, 6-8 December 1999. Geneva, World Health Organization**:** 43 p. + annexes., WHO and March of Dimes (2006). Management of birth defects and haemoglobin disorders : report of a joint WHO-March of Dimes meeting, Geneva, Switzerland, 17-19 May 2006. Geneva, World Health Organization**:** 27 p.) and reviews (Christianson, A. and B. Modell (2004). "Medical genetics in developing countries." Annu Rev Genomics Hum Genet **5**: 219-265.,Christianson, A., C. P. Howson and B. Modell (2006). "March of Dimes: global report on birth defects, the hidden toll of dying and disabled children." March of Dimes: global report on birth defects, the hidden toll of dying and disabled children.).

Limitations of the Global Database

Currently the Database includes only early-onset congenital disorders (i.e. those that usually present before 20 years of age[5]). It does not (yet) include congenital disorders caused by environmental risk factors such as maternal exposure to infection[6], malnutrition, or teratogens, because their epidemiology is not susceptible to the form of modelling currently used. Conventional methods such as local ongoing surveillance or periodic surveys are required to map their epidemiology, because exposure to risk, and hence birth prevalence, varies with place, time, and deployment of interventions including immunisation, nutritional supplementation, restriction of exposure to teratogens and diagnosis and treatment for the mother before or during pregnancy.

We emphasise here that the Global Database does not pretend to provide accurate figures. Rather, it aims to provide a framework for objective assessment of the global, regional and national burden of congenital disorders, and to generate provisional estimates that are sufficiently evidence-based to fill the void caused by the absence of observational data, and so remove the impasse to policy and service development that often results.

The general argument

Policymakers need information in order to make decisions. They prefer clear, unambiguous, agreed evidence that covers, in this case:

- The scale of the problem before them – baseline birth prevalence (incidence). [7]
- Outcomes in the absence of intervention.
- Available interventions and their potential effects.
- The current country (or regional) situation with respect to deployment of interventions, and current outcomes.
- Future projections (a) with current policies, (b) with policy changes.
- For each potential intervention, an objective appraisal of the difference that deployment might make in terms of human and financial costs and benefits.

Figure 1.2 shows the life-time trajectory of any constitutional congenital disorder. Outcomes in the absence of care are shown in blue, interventions and additional outcomes are shown in red.

[5] This is the upper limit for the source data published by Baird, P. A., T. W. Anderson, H. B. Newcombe and R. B. Lowry (1988). "Genetic disorders in children and young adults: a population study." Am J Hum Genet **42**(5): 677-693.
[6] For a brief discussion of congenital disorders due to maternal infection see *Annex A2: Environmental disorders*. European registry data indicate that congenital infections account for around 1% of congenital anomalies in high income settings. Obviously the rate is far higher in most lower-income settings.
[7] This is the essential starting point for assessing service needs and the potential and actual effect of interventions.

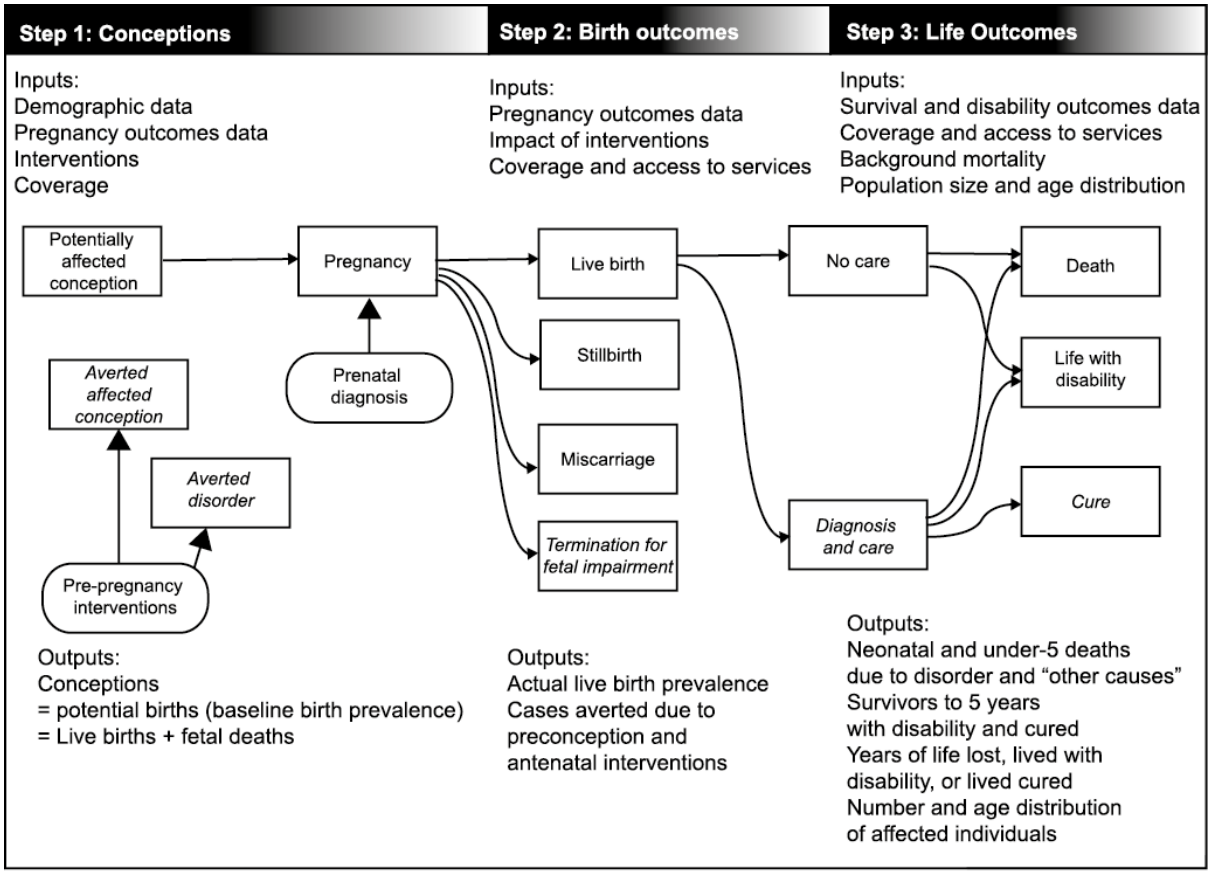

Figure 1.2. Chart showing the sequence of events covered in the Global Database. Boxes represent data points, of which those linked to rounded lozenges representing possible interventions enumerate their main outcome types.

We propose that sufficient demographic and disorder-specific data exist or can be inferred to quantify each step in the trajectory for each group of constitutional congenital disorders, and so to meet many of the information needs of policy-makers at the country level.

- Country-specific global demographic estimates including annual births are available from UN World Population Prospects (WPP)[8].
- The birth prevalence in the absence of any intervention (baseline birth prevalence) of the main groups of constitutional congenital disorder is known or can be estimated.
- The effects of implementing available interventions have been recorded.
- Birth outcomes, and outcomes for live-born children with no care and with optimal care are known or can be estimated.
- The proportion of a population with access to optimal services can be estimated using infant mortality as an indicator.
- By integrating these data, it is possible to generate comprehensive epidemiological estimates at the country level that are – in the broadest sense – evidence-based. These can then be aggregated in a variety of ways to yield regional and global estimates.[9]

[8] http://esa.un.org/unpd/wpp
[9] Possible application of the method at the sub-country (e.g. administrative) level is being investigated.

Outputs from the Global Database

The following outputs are selected to inform service planning.

Baseline birth prevalence (prevalence in the absence of any intervention)

This is the foundation of the Global Database, because

- It is the most strongly evidence-based of all inputs
- It provides an envelope that must be filled by all estimated outcomes.

Outcomes to age 5

Estimated outcomes are particularly reliable to age 5, for the following reasons.

- Birth outcomes (termination of pregnancy, fetal death, live birth) are recorded in many congenital anomaly registries.
- The literature contains substantial data on survival to age 5, but observational data on full long-term survival is limited.
- Since mortality due to congenital disorders is highest in the early years, survival with disability to age 5 may be taken as an indicator of long term service needs.
- Disability is arguably of even greater significance than early mortality in terms of service needs.

The table shows key outputs to age 5, selected for publication on the Web.

Table 1.1 Key outputs to age 5 from the Global Database, for each disorder group.

BASELINE birth prevalence, i.e. if no intervention.	Estimated NO-CARE outcomes at age 5 (outcomes in the absence of any intervention)	Estimated ACTUAL outcomes at age 5, 2010-14 (outcomes with current interventions).
1. Total affected births (live births & stillbirths) /1,000 births. This is the BASELINE RATE: all outcomes must fit within this envelope.	2. Fetal deaths 3. Under-5 deaths attributable to the disorder 4. Under-5 deaths due to other causes 5. Survivors at 5 years living with disability	6. Reduction due to pre-pregnancy intervention 7. Reduction due to termination of pregnancy (TOP) 8. Actual fetal deaths 9. Actual under-5 deaths attributable to the disorder 10. Actual under-5 deaths due to other causes 11. Actual survivors at 5 years living with disability 12. Actual survivors at 5 years effectively cured
	The sum of 2-5 above equals the BASELINE.	The sum of 6-12 above equals the BASELINE

There are inevitably many inaccuracies in the numerous inputs used to achieve these estimates. However the rule remains that all outcomes must fill the envelope of baseline birth prevalence. Thus for example, under-estimation of termination of pregnancy will lead to over-estimation of early mortality; over-estimation of early mortality will lead to under-estimation of disability or cure. Despite such variation, all the outcomes listed are important for health services, and cannot be discounted or ignored.

Long-term outcomes

These estimates are based on projected long-term survival, for which the evidence is often weaker. They include:

- disorder-specific mean life expectancy by country
- estimated months (or years) of life lost, or lived with disability, due to each disorder.
- estimated current patient numbers with each disorder, and their age distribution

Purpose and organisation of this series of articles

This set of thirteen articles describes how input data are obtained and handled, in sufficient detail to enable the development of similar country or regional databases. Since the method requires integration of data from many different sources, some articles are unavoidably weighty. The first five articles cover methods that are common for all disorder groups and the remainder address aspects specific for individual disorder groups, as follows.

- Part I. General Method
    - Article 1: Introduction: scope and general overview (this article).
    - Article 2: Core methods for estimates to five years of age.
    - Article 3: Methods for generating long-term estimates.
    - Article 4: Uses of demographic and geographic data
    - Article 5: Estimating access to services
- Part II. Congenital anomalies
    - Chromosomal disorders. Estimating birth prevalence and outcomes
    - Congenital malformations 1. Estimating birth prevalence and birth outcomes
    - Congenital malformations 2. Estimating outcomes of live births
- Part III. Genetic disorders
    - Haemoglobin disorders. A model for single gene disorders
    - Rare single gene disorders[10]. Estimating collective birth prevalence and outcomes
    - Consanguinity-associated disorders. Estimating collective birth prevalence and outcomes
    - Rhesus haemolytic disease. Estimating birth prevalence and outcomes
    - G6PD deficiency neonatal jaundice. Estimating numbers at risk

These articles together with their Annexes give full details of the method used, plus examples of outputs, chosen to illustrate the potential of the method and summarised by WHO Region. Further data including selected country-specific estimates are available online at www.mgdb.info.

The need for an agreed terminology

Evidence supporting policy-making should be presented using clear, unambiguous and uncontroversial terms that are suitable for a multidisciplinary audience. For effective handling at the public health level congenital disorders must be bundled into manageable and clearly defined groups. The construction of a quantitative database requires clear definition of each item included, but we encountered many examples of ill-defined terminology while building the Global Database. To enable the work to go forward, it proved necessary to create a set of terms and definitions appropriate for use in Community Genetic epidemiology. These terms are used throughout this series of articles, and they are defined at first use either in the text or in a footnote. They are listed fully below with the aim of stimulating discussion, and initiating an agreed terminology suitable for use in Community Genetics.

[10] A collective term used in the Global Database for dominant, recessive and X-linked single gene disorders whose prevalence is determined by a balance between new mutation and natural selection, and so are expected to have similar collective birth prevalence world-wide.

The lack of agreed terminology arises because the diversity of congenital disorders has led to the development of disparate - often disease-specific - clinical services.[11] Clinical service fragmentation in turn leads to fragmentation of concepts, promotes competition rather than collaboration to achieve a consensus, and creates intellectual and practical problems in handling congenital disorders as a group. To take just one example, the fact that the terms congenital *anomaly* and congenital *disorder* are often, mistakenly, treated as equivalent has contributed to widely divergent estimates of the global burden of congenital disorders, and can cause confusion and paralysis for policy-makers.

Figure 1.3 shows the main disorder groups covered by the WHO definition of congenital disorders, and the different ways in which they are bundled by different professional groups.[12]

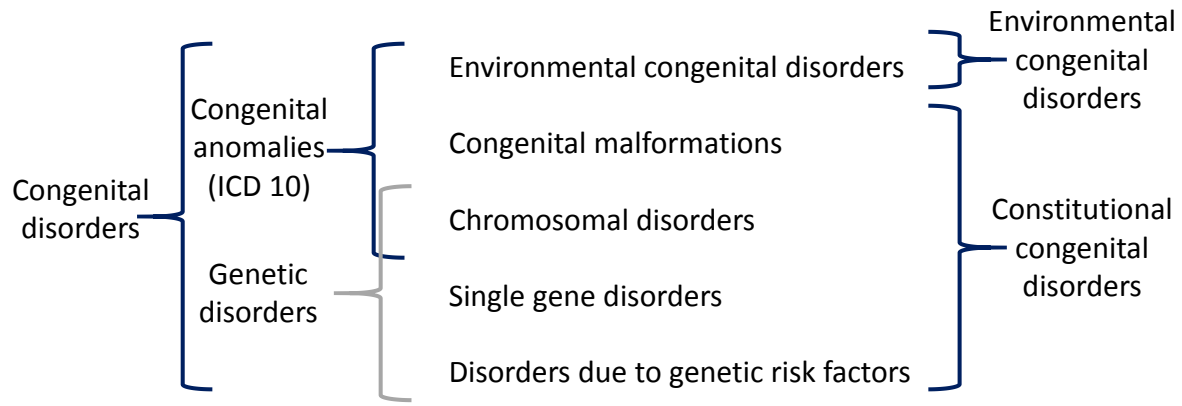

Figure 1.3. Bundling of the main groups of congenital disorder used for different professional purposes. The WHO definition is shown on the left. The ICD10 definition of congenital anomalies includes only disorders with structural effects and excludes the majority of genetic disorders. Genetic disorders include chromosomal disorders but exclude environmental disorders and most congenital malformations. The bundling used here into environmental and constitutional congenital disorders is shown on the right. The bundling used by Rare Diseases organisations (e.g. globalgenes.org) includes some disorders in all groups.

The term *congenital anomaly* applies for congenital disorders with structural effects, regardless of cause, and so includes cases in all major groups though malformations and chromosomal disorders predominate. They are sufficiently clearly delineated at a practical clinical level to be recorded in formal congenital anomaly registries and to have their own chapter in ICD10 - Chapter XVII “congenital malformations, deformations and chromosomal abnormalities” (formerly the Q chapter). The ICD10 classification greatly facilitates collective recording and tracking and, together with the availability of quantitative data from registries, gives congenital anomalies a relatively high profile in a public health context. This has the advantage that high quality prevalence data are readily available, but the disadvantage that these data may be interpreted as describing the totality of congenital disorders.

In contrast, the scattering of single gene disorders[13] throughout the ICD system makes them difficult to grasp collectively, and they are often seen as too diverse and individually rare to be worthy of consideration at a public health level. However single gene disorders are estimated to account for over 30% of congenital disorders world-wide (Christianson and Modell 2004) so this omission is unacceptable. The Global Database uses a collective quantitative approach for single gene disorders derived from the fundamental principles of

[11] For example there is usually little contact between specialist services for haemophilia, phenylketonuria, cystic fibrosis and haemoglobin disorders though all are common single gene disorders.
[12] Confusion is sometimes avoided by calling the entire group “congenital and genetic disorders”. However cumbersome usage is best avoided, especially when addressing a non-specialist audience.
[13] Disorders caused by DNA variants with strong effect. They follow Mendelian inheritance patterns (dominant, recessive, X-linked: most individuals with the relevant variant (or combination of variants) develop the disorder.

population genetics (see *Article 10: Single gene disorders*). In addition, as a place-holder for the large but still diffuse category of disorders due to genetic risk factors,[14] it includes three well-understood risk factors – rhesus negativity, G6PD deficiency and alpha plus thalassaemia.

The distinction between environmental and constitutional congenital disorders on the right of Figure 1.3 and used here cuts across the traditional bundling on the left. Clearly the distinction is not absolute: some disorders classed as constitutional may also be strongly influenced by environmental factors, and environmental influences often interact strongly with genetic predisposition[15]. Rather, as is common in medicine, the distinction is a pragmatic one enforced by the fact that the current Global Database method can be used only for disorders with a predictable baseline birth prevalence.

Divergent estimates of under-5 deaths due to congenital disorders

Terminological confusion is partly responsible for a wide discrepancy between estimates of global early mortality due to congenital disorders.

It is widely recognised that the average baseline birth prevalence of constitutional congenital *anomalies* is at least 20/1,000 (Czeizel and Sankaranarayanan (1984), WHO (1985a), Baird, Anderson *et al.* (1988)), while the baseline birth prevalence of congenital *disorders* (including single gene disorders and early-onset disorders due to genetic risk factors) is over 37/1,000 (Christianson, Howson *et al.* 2006). Their contribution to early death and disability is masked by high early mortality from other causes in lower-income settings, but it is estimated that infant mortality can fall below 10/1,000 only when interventions for prevention and care are in place (WHO (1985a), Christianson, Howson *et al.* (2006). Consequently congenital disorders would be expected to hold a significant place in global health policy-making[16], but they are not mentioned at all in recent reviews of global early mortality such as Mathers and Loncar (2006) and (Black, Cousens *et al.* 2010).

Estimates of global under-5 deaths due to congenital *anomalies*[17] in 2000-2001 were 3.3/1,000 births (4.1%) from the Global Burden of Disease (GBD) study (Lopez, Mathers *et al.* 2006), 2/1,000 from WHO (Liu, Johnson *et al.* 2012), and 9-10/1,000 (12-13%) from the March of Dimes (Christianson, Howson *et al.* 2006).

Table 1.2 compares more recent estimates. The GBD estimate for congenital *anomalies* in 2013 (www.healthdata.org) at 3.7/1,000 births is around half the Global Database estimate.

Furthermore, GBD's use of the term "congenital" to cover congenital anomalies gives the misleading impression that GBD estimates apply for all congenital disorders. Table 1.2 shows GBD estimates for "congenital" under-5 deaths are only a quarter of the Global Database estimates for total congenital disorders (for details see Annex A1: Comparison of GBD and Global Database under-5 mortality estimates) .

[14] A DNA variant that is usually harmless but can interact with other genetic and environmental factors to cause a clinical disorder. Many common DNA polymorphisms with weak effects on health fall into this category.
[15] For example the birth prevalence of neural tube defects is strongly influenced by maternal vitamin intake, so many cases could be classed as due to genetic risk factors. Here they are classed as constitutional because (a) no normal diet contains enough natural folate to completely prevent them and (b) there is as yet insufficient evidence to split this clearly-defined malformation group by cause.
[16] For example the UN 4th Millennium Development Goal (to reduce the under-5 mortality rate by two-thirds, www.un.org/millenniumgoals) and WHO's strategy for non-communicable diseases (www.WHO.int).
[17] It is only possible to compare estimates for congenital anomalies because, with the exception of haemoglobin disorders, single gene disorders are not included as a category in the GBD.

Table 1.2. Contrasting estimates of the contribution of congenital anomalies and congenital disorders to global under-5 deaths in 2013

World rates for 2013	GBD congenital anomalies	Global Database	
		Congenital *anomalies*	Congenital *disorders*
Total births, 1,000s	136,110		
World under-5 deaths	8,001,839		
"Congenital" under-5 deaths /1,000	3.7	8.0	15.0
Annual "congenital" under 5 deaths	503,609	1,088,883	2,041,656
"Congenital" under-5 deaths % of total	6.3	13.6	25.5

The Global Database is the product of an international collaboration aiming to improve the quality and availability of evidence on the birth prevalence and outcomes of congenital disorders.

Reasons for divergent estimates

The wide divergence between different authoritative estimates of the contribution of congenital disorders to the global burden of disease makes it necessary to consider possible reasons for over- or under-estimating their significance.

Possible reasons for over-estimation

In response to a letter in the Lancet (Modell, Berry *et al.* 2012), Liu, Cousens *et al.* (2012) listed six possible reasons for over-estimation of under-5 mortality due to congenital anomalies:

- unrepresentatively high prevalences based on biased samples
- effects of different fertility patterns or genetic and environmental contexts
- inclusion or otherwise of stillbirths and terminations of pregnancy
- risks of double-counting
- shortage of population-based, cause-specific fatality rate data for varying care settings
- inclusion of deaths of affected children due to other causes

In revising the Global Database, great care has been taken to exclude these possible sources of error and they do not significantly affect current estimates of under-5 deaths due to congenital anomalies. However, the discrepancy between the revised Global Database and GBD estimates remains as wide as ever.

Possible reasons for under-estimation

There is good general agreement between Global Database and GBD estimates of under-5 deaths due to congenital anomalies for high income countries. However GBD estimates are far below Global Database estimates for most middle and low income countries (see Annex A1: Comparison of GBD and Global Database under-5 mortality estimates). This is the explanation for the difference between the global estimates, and for our conclusion that the global burden of congenital disorders is grossly underestimated. Many different factors may contribute to this under-estimation.

Requirements for correct diagnosis

Only a minority of congenital disorders are obvious at birth, and accurate diagnosis frequently requires resources that are not available in lower-income settings. Therefore little reliable prevalence data are available for lower-income countries. In the absence of data it is easy to assume that the problem is not significant, or that there is no evidence to support service planning.

Difficulty in defining cause of death

Reliable, medically-certified cause of death data can only be obtained in high income settings with low mortality due to congenital disorders because prevention and care are also available. In lower-income settings deaths due to congenital disorders are likely to be mis-attributed to other causes, such as infection. Therefore if observed medically-certified death rates are applied globally, early deaths due to congenital disorders will be greatly under-estimated.

Perceived low prevalence in high income settings

Congenital disorders are generally perceived to be rare in high income settings because (a) the present high income countries had the lowest baseline birth prevalence of congenital disorders to start with; (b) the birth prevalence of some groups has been greatly reduced by interventions such as anti-D for rhesus negative mothers, and prenatal diagnosis with the option of termination of pregnancy; (c) death and disability due to some groups has been greatly reduced by early diagnosis and successful treatment (e.g. paediatric surgery).

Since it is death and disability that bring disorders to the attention of health services, their perceived prevalence in high income settings is now far below their actual birth prevalence. Because so many academic/medical policy-makers come from, or were trained in high income countries this biased perception tends to be extended globally.

Reliance on the International Classification of Diseases (ICD)

The fact that congenital disorders are collectively common but individually rare presents difficulties in grasping them collectively. ICD is a common starting- point for epidemiological undertakings, and the placing of conditions within it can affect their perceived importance. The fact that chromosomal disorders and congenital malformations are grouped together under the heading of congenital anomalies in ICD10 chapter XVII (the Q chapter) provides a convenient handle for addressing this group collectively at the public health level. By contrast single gene disorders, which contribute almost half of all congenital disorders, are scattered throughout the ICD system and are usually perceived as too diverse and individually rare to handle collectively.[18]

Fragmentation of clinical services

Because of their extreme clinical diversity, management of genetic diseases requires diverse interventions involving numerous different services. Fragmentation of clinical services exacerbates the problem of handling these disorders as a group.

Failures in professional communication

The specialist literature contains extensive information on the nature, prevalence and outcomes of congenital disorders, but this is inadequately reflected in the public health literature – the specialist community has failed to communicate with the public health community.

The Global Database is designed to overcome the problems that lead to under-estimation of the collective public health importance of congenital disorders, by helping to bridge the gap between public health and existing specialist knowledge.

[18] In recent years this problem has led to the development of the Rare Diseases community, e.g. https://rarediseases.org, www.raredisease.org.uk

1.2 Notes on terminology and definitions of terms used in the Global Database

General principles

Progress in any discipline requires agreement between professionals on the meaning of the terms used. The first part of this Introduction clearly demonstrates the need for consideration and agreement on terminology. A first step could be to agree on standards for communication in community genetics.

Standards for communication– initial suggestions

Terms used must take account of the audience to be addressed. For example, the current enterprise aims to harmonise specialist medical genetic information with public health objectives. The target audience is therefore multidisciplinary, ranging from directors of public health to primary health care practitioners, politicians, the media and patient support associations. The same principle applies for the whole of Community Genetics, since the defined aim is to make genetic information and services available to all who may benefit.

Therefore agreed, clear and simple terms must be used: (a) to enable communication among health professionals working in different disciplines; and (b) to support health professionals to provide correct and consistent information to others. Therefore -

Each term used must be:

- precise but comprehensible
- transparent, and accurate in its clinical implications
- sensitive to the preferences of users, especially patients

Additionally

- terms used should as far as possible apply across the full spectrum of congenital disorders
- terminology should be harmonised internationally
- consideration should be given to translation into the vernacular

Selection of terms used in the Global Database

In the course of developing the Global Database, it was necessary to find terms that precisely define each element included in the calculations. All such terms, as used in the Database, are listed below.

We use existing specialist terminology as far as possible, but it sometimes proved necessary to find alternative terms to (a) meet the specific requirements of the database, (b) facilitate communication with public health practitioners and (c) take account of the general requirements for multi-disciplinary communication. In some instances the terms used to meet these requirements differ from those conventionally used by specialists.

We therefore emphasise that:

- The definitions listed here are presented exclusively in order to describe their use in building the Global Database, and in the accompanying documents.
- There is no intention to alter existing specialist usage: we are not proposing the terms listed should be generally adopted.
- Our experience of the need for agreed definitions does point to some inconsistencies in current usage: the terms listed could perhaps contribute to (hypothetical) future discussion aiming to harmonise current usage.

- We also offer this list of definitions in the hope of stimulating debate about terms for future use in the broad context of Community Genetics.

Requirements for multidisciplinary communication

Community genetics aims to support the incorporation of genetic approaches into medical practice. The target audience therefore includes everyone involved in developing policies for reproductive health and paediatric services – a wide range of health professionals, members of lay support groups, politicians, educators and journalists. However many terms relating to congenital disorders were designed for specialist use and may not be readily understood by a more general audience. Though it is not possible to avoid the use of technical terms, we consider it desirable to adjust some conventional specialist terms for use in the multidisciplinary context of Community Genetics.

The technical terms used in these articles aim to comply with the following rules for multidisciplinary communication.

- All technical terms should be as precise, simple and clear as possible, and free of unintended bias.
- Abbreviations and acronyms should be avoided as far as possible.
- Technical terms should be defined in the text and/or a footnote when first used.
- A Glossary should be provided.

The following list is intended to include all technical terms used in this series of articles, together with a discussion of the reasons for selecting them when this is indicated. Creation of the list and definition of terms is a work in progress. All terms are proposed with the aim of obtaining wide consultation. To facilitate review and consultation, terms are grouped under broad headings rather than listed alphabetically.

Specific terms

Congenital disorders

Disease/disorder/defect/condition?

To what extent are these terms equivalent, and which should be chosen for use in Community Genetics? In the Global Database the term *disorder* is generally used in preference to disease to refer to a condition that can lead to death or disability, because this is the term that many patients prefer. Not all congenital heart defects cause death or disability: the Global Database identifies those that cause death or disability as congenital heart *disease*. The term condition is not used as it can cover almost any phenotype regardless of whether or not it causes death or disability.

Congenital disorder (Birth defect)

“Any potential pathological condition arising before birth --- whether it is evident at birth or becomes manifest later in life.” (WHO (1985a) and (2000), WHO and March of Dimes (2006)). This definition includes environmental congenital disorders, congenital malformations, single gene disorders, chromosomal disorders and disorders due to genetic risk factors (see definition below). The term congenital anomalies is often, mistakenly, used as equivalent to congenital disorders.

Congenital anomaly

A disorder included in Chapter XVII (formerly the Q chapter) of ICD 10 – “Congenital malformations, deformations and chromosomal abnormalities”. This chapter includes congenital disorders with structural effects regardless of cause. It does not include the majority of single gene disorders and disorders due to genetic risk factors.

The term *congenital anomaly* is often, mistakenly, understood to be equivalent to *congenital disorder*. (See e.g. Wikipedia article on congenital disorders; WHO short document on pre-pregnancy care; British and Irish Network of Congenital Anomaly Researchers (BINOCAR) – "A congenital anomaly is defined as any defect present at delivery, probably originating before birth, and includes structural, chromosomal, genetic and biochemical defects and malformations."

Congenital anomaly registry

A system for collecting data on the birth prevalence of congenital anomalies. Most registries also record birth outcomes. Conditions included are usually limited to those listed in the chapter XVII (the Q chapter) of ICD10, with some exclusions. Many, but not all congenital anomaly registries contribute to umbrella registries such as EUROCAT[19] or ICBDSR[20]. The reports of the umbrella registries giving details of participating registries show wide differences in opportunities, and methods used, for collecting data.

Umbrella registry

A registry that collects data from a number of contributing registries in a standardised format. The two umbrella registries used in the Global Database are the European Surveillance of Congenital Anomalies network (EUROCAT) and the International Clearing House for Birth Defects and Research (ICBDSR). For UK, see The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS). Public Health England

Environmental congenital disorder

A congenital disorder due to one or more external risk factors such as maternal exposure to infection, malnutrition, or teratogens. Any organ system, or multiple systems may be implicated. Their birth prevalence can be greatly reduced by conventional public health measures including immunisation, restriction of exposure to teratogens, nutritional supplementation, or diagnosis and treatment during pregnancy. The borderline between environmental and constitutional congenital disorders is not clear-cut, e.g. a proportion of neural tube defects (and oro-facial clefts, and possibly some other malformations) are avoided by folic acid food fortification.

Constitutional congenital disorder

A congenital disorder (mainly) due to an endogenous rather than an environmental cause. This definition includes most congenital malformations, chromosomal disorders, single gene disorders, and disorders due to common genetic risk factors. The borderline between environmental and constitutional congenital disorders is not clear-cut (see above).

Sporadic congenital disorder

A congenital disorder that can arise in any pregnancy, without known environmental or genetic cause. This definition applies to most congenital malformations and chromosomal disorders. It also includes disorders with functional rather than structural effects and no known cause (e.g. cerebral palsy arising before birth).

Congenital disorders, age at onset

Early onset = congenital disorders that usually present before puberty: disorders initially treated by paediatricians[21]. Later onset = congenital disorders that usually present in adult

[19] EUROCAT: European Surveillance of Congenital Anomalies. Eurocat-network.eu
[20] International Clearinghouse for Birth Defects. www.icbdsr.org
[21] The paediatric upper age limit is often defined as 12 years, but is often considerably higher, especially when a disorder involved delayed or absent puberty. For example Baird et al (1988) use an age limit of 20 years: the rates presented are used in the Global Database because the great majority of the disorders included present before 12 years of age. Bittles, A. H. and J. V. Neel (1994). "The costs of human inbreeding and their implications for variations at the DNA level." Nat Genet **8**(2): 117-121. and Bittles, A. H. and M. L. Black (2010a). "Evolution in health and medicine Sackler colloquium: Consanguinity, human evolution, and complex diseases." Proc Natl Acad Sci U S A **107 Suppl 1**:

life, e.g. family cancer syndromes, genetically-determined neurodegenerative disorders, cardiovascular disease due to bicuspid aortic valve.

Severe congenital disorder

A congenital disorder that causes premature death or disability in the absence of intervention. (In genetic counselling, it is up to informed parents to assess the severity of a disorder in the context of their individual medical, social and economic situation.)

Lethal congenital disorder

Disorder for which treatment is ineffective, that almost always causes early death (e.g. anencephaly, bilateral renal agenesis, alpha thalassaemia hydrops fetalis).

Potentially lethal congenital disorder

Disorder that is highly likely to cause early death in the absence of care, but may be either corrected or greatly ameliorated by optimal care (e.g. many types of congenital malformation, haemoglobin disorders, phenylketonuria, cystic fibrosis).

Usually sub-lethal congenital disorder

Disorder that, untreated, causes disability but permits long-term survival (e.g. most malformations of the limbs or genitalia).

Chromosomal disorders

Naming of chromosomal disorders in the Global Database

Trisomy 21: The professionally-agreed term is Down syndrome, and this is used in the Global Database. However it may also be called Down's syndrome (perhaps in response to expressed preference of lay support groups). For example, official groups in the UK include the Down's Syndrome Association, the UK Down Syndrome Cytogenetic Register (DSCR), and the National Down's syndrome screening programme.

Other trisomies: Trisomy 13: Patau syndrome, and Trisomy 18: Edwards syndrome.

Other autosomal (also called "rare chromosomal disorders"): Includes other disorders of chromosome number (triploidy, other trisomies) and chromosomal rearrangements. The group is described quantitatively by Wellesley, Dolk *et al.* (2012).

Sex chromosome disorders: XO: Turner syndrome, and XXY: Klinefelter syndrome.

Congenital malformation

A congenital physical anomaly that is deleterious, i.e. a structural defect perceived as a health problem. (Dictionary: irregular, anomalous, abnormal, or faulty formation or structure).

Isolated congenital malformation

One or more malformation(s) within one organ system (EUROCAT definition). The definition covers several different malformations affecting the same system, e.g. several different congenital heart defects.

Single isolated congenital malformation

A congenital malformation affecting only one part of an organ system. For example, many malformations of the heart involve more than one part of the organ – e.g. the ventricular septum plus one or more of the cardiac valves. EUROCAT defines malformations affecting one or more components of the heart but not associated with a defect in any other organ

1779-1786. describe "pre-reproductive mortality" associated with parental consanguinity, without specifying an age limit: their rates are used in the Global Database to represent the consanguinity-associated increment in under-5 mortality in the absence of care, because in this situation most deaths due to recessive disorders occur before 5 years of age.

system as “isolated congenital heart defects”. By contrast, a defect in only one component of the heart is defined as a “single isolated congenital heart defect” (Garne 2013).

Chromosomal-associated congenital malformations

Congenital malformations that form part of a chromosomal syndrome e.g. over 30% of Down syndrome cases are associated with congenital malformations, mainly congenital heart disease. Patau and Edwards syndromes are always associated with malformation. Less severe congenital malformations are also common in Turner syndrome.

Non-chromosomal congenital malformations

Congenital disorders that remain when chromosomal-associated cases are subtracted.

Non-syndromic congenital malformations

Congenital malformations that are not associated with chromosomal disorders, single gene disorders or genetic syndromes, and not due to environmental factors – i.e. cases with no known cause. In reports on the epidemiology of congenital malformations affected birth prevalence is ideally described in terms of total and “non-syndromic” cases (e.g. birth prevalence of oro-facial clefts in China and Latin America).

ICBDSR and EUROCAT (to 2015) provide data for total and non-chromosomal congenital malformations. Non-syndromic congenital malformations are calculated by subtracting cases due to environmental causes, single gene disorders and genetic syndromes. In 2015 EUROCAT changed to reporting total and “non-genetic” malformations. To obtain non-syndromic congenital malformations cases with environmental causes must be subtracted.

Associated congenital malformations

Malformations that occur in two or more organ systems in the same individual. Around 16% of non-syndromic malformations are associated, i.e. contribute to multiple malformations, so that for every 100 malformations reported there are around 84 affected individuals. In EUROCAT data, average association rates are 16% for total non-syndromic malformations, 11% for malformations in live births, 44% in fetal deaths/ stillbirths and 37% in terminations of pregnancy for fetal impairment.

Multiple malformations (Multiple congenital anomalies – MCAs)

Two or more major (i.e. life threatening, severely disabling, or requiring substantial medical care) unrelated defects of unknown aetiology in the same fetus or infant[22].

Additional conditions

A category included in the Global Database to accommodate non-genetic congenital disorders that are perceived as congenital disorders by paediatricians but are not included in congenital anomaly registries because: (a) they are classed elsewhere in ICD10 (e.g. congenital hypothyroidism due to thyroid aplasia or dysplasia); (b) they cause functional rather than structural abnormality (e.g. cerebral palsy); or (c) they have uncertain status (e.g. pyloric stenosis).

The three disorders currently included in the Global Database (congenital hypothyroidism due to thyroid a/dysplasia, pyloric stenosis, prematurity-related persistent patent ductus arteriosus) may all be bundled with congenital malformations for summary purposes.

Rare diseases

(Wikipedia, March 2016)

- In the United States, the Rare Diseases Act of 2002 defines rare disease strictly according to prevalence, specifically "any disease or condition that affects fewer than

[22] www.icbdsr.org

200,000 people in the United States," or about 1 in 1,500 people. (This definition is essentially like that of the Orphan Drug Act of 1983, a federal law that was written to encourage research into rare diseases and possible cures.) (Comment: a major shortcoming of this approach is that, as the total population increases, the denominator and hence the prevalence changes, e.g. the US population increased from 234m in 1983, to 321m in 2016. Over the same time period a similar but opposite effect has occurred in Japan, with a secular decline in population).

- In Japan, the legal definition of a rare disease is one that affects fewer than 50,000 patients in Japan, or about 1 in 2,500 people.
- The European Commission on Public Health defines rare diseases as "life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them". The term low prevalence is later defined as generally meaning fewer than 1 in 2,000 people. (Diseases that are statistically rare, but not also life-threatening, chronically debilitating, or inadequately treated, are excluded from their definition.) The European Organization for Rare Diseases (EURORDIS) also includes both rare diseases and neglected diseases into a larger category of "orphan diseases".

Comment. Almost all *definitions of rare diseases are based on prevalence in the population rather than birth prevalence*. Therefore when survival improves as a result of care, disorders may move out of the category – e.g. sickle cell anaemia might be classed as rare in some sub-Saharan African countries where birth prevalence is high, but not-rare in North America where birth prevalence is far lower.

The effective mingling of rare genetic disorders and communicable diseases ranging across malaria, leprosy, TB etc. is understandable in promoting the care needs of people with all forms of rare diseases, and their families. But from diagnostic, genetic educational and genetic counselling perspectives it can create a major problem. The more so when the prevalence of communicable diseases in high and low income countries (even communities) varies greatly. Additional controversy exists as to whether all rare diseases should be bundled together, e.g. <1/2,000, or into 'rare' (<1/2,000) and ultra-rare (<1/100,000?).

Genetic disorders

Genetically-determined disorders

Collective term for single gene disorders, chromosomal disorders and disorders due to genetic risk factors. This is an imprecise and potentially confusing term that groups disorders with a clear-cut genetic cause (chromosomal and single gene) with a potentially very large group of "disorders due to genetic risk factors" whose boundaries have not yet been defined (see definition of term). Therefore, this collective term is not used in the Global Database or the Methods articles.

Single gene disorders

Disorders caused by DNA variants with strong effect. They follow Mendelian inheritance patterns (dominant, recessive, X-linked): most individuals with the relevant variant (or combination of variants) develop the disorder.

- Dominant single gene disorders. Most individuals with one copy of the gene variant develop the associated disorder.
- Recessive single gene disorders. This term usually only applies for disorders caused by DNA variants of the autosomes. Individuals who inherit one gene variant for a recessive disorder are unaffected. Most individuals who inherit two gene variants for the same recessive disorder develop the disorder.
- X-linked single gene disorders are due to DNA variants on the X chromosome. Most males whose single X chromosome carries the relevant gene variant develop the

disorder. Most females in whom only one X chromosome carries the relevant variant are unaffected. Females who inherit two copies of the relevant variant may develop the disorder.

Autosomal dominant and autosomal recessive disorders

The terms dominant and recessive are often pre-fixed with “autosomal” to distinguish them from X-linked dominant and recessive disorders. The autosomal prefix is not used in the Global database for three reasons that take account of the need to clearly define every term used for a multidisciplinary audience. (1) When grouping single gene disorders the priority focus is on inheritance pattern, independent of the arrangement of genes on chromosomes. The *autosomal* prefix should only be used when the intended audience already has a clear understanding of the relationship of genes and chromosomes. Otherwise the inclusion of chromosome-specific terms can cause confusion. (2) The terms dominant and recessive do not strictly apply for most X-linked disorders because random X-chromosome inactivation can lead to manifestation of the disorder in female heterozygotes. (3) Cumbersome terminology should be avoided as far as possible.

Therefore the Global Database uses the simple terms dominant, recessive and X-linked disorders.

Rare single gene disorders

A collective term for dominant, recessive and X-linked single gene disorders that are disadvantageous without any compensating selective advantage. Such disorders are expected to have similar collective birth prevalence world-wide, because their gene frequency is determined by a balance between new mutation rate and natural selection, neither of which vary greatly between populations (see *Article 10: Single gene disorders*).

Consanguinity

The term consanguineous simply means related by blood. Consanguinity refers to the state of being related by blood. In medical genetics, the term refers to the relationship between people who are second cousins or closer. However in a health context the term “consanguinity” is often used to mean a consanguineous union. This usage should be avoided in the interest of clarity. We suggest the following terms.

- *Consanguineous union* = the relationship between blood relatives who have children together, whether married or not.
- *Parental consanguinity* = a general term for use when discussing the implications for an individual or group, of a consanguineous relationship between their parents.

In populations where most couples marry, the term consanguineous *marriage* is often used to describe a union between blood relatives. The term *cousin marriage* is also used in populations where consanguineous unions involve cousins but e.g. uncle/niece marriage is excluded. We aim to avoid using these terms in the global context of Community Genetics.

Consanguinity-associated disorders

A collective term for the increment in congenital disorders associated with parental consanguinity. The increment is mainly due to increased birth prevalence of recessive single gene disorders. Consanguinity-associated disorders should not be called *disorders due to parental consanguinity*. They are due to the inheritance of two recessive gene variants that can cause the same disorder. Parental consanguinity increases the chance that a couple will both carry the same recessive gene variant. It does not in itself cause any medical problem.

Haemoglobin disorders (haemoglobinopathies)

Disorders caused by variants of the haemoglobin genes. These are called haemoglobinopathies by specialists, but most non-specialists find this term

unpronounceable. The English translation, haemoglobin disorder, is preferable for multidisciplinary use.

Multifactorial disorder

A term used for clinical categories of disorder with genetic, environmental and unknown causes, especially when these are obscure or ill-understood. Most "multifactorial disorders" include a relatively small group of single gene disorders, some with both genetic and environmental causes, and some with purely environmental causes. As an example, congenital malformations are often described as multifactorial disorders: the proportion due to environmental causes falls with improving public health; a handful are due to single gene disorders; some (vitamin-sensitive malformations) are due to both genetic and environmental causes; the majority are due to sporadic accidents in embryonic development. The term can be confusing, as it is often mistakenly understood to imply genetic/environmental interaction in most cases. It is not used in the Global Database because it tends to obscure rather than clarify understanding of cause.

Genetic risk factor

A DNA variant that can interact with other genetic and environmental factors to cause a clinical disorder. Many common DNA variants (genetic polymorphisms) may have weak effects on health and so fall into this category. Some such variants have very clear-cut effects in the sense that the disorder concerned can only arise if a specific risk factor is present (e.g. rhesus haemolytic disease of the newborn, the common forms of haemoglobin H disease). However most genetic risk factors increase the chance that a given clinical disorder will arise, e.g. G6PD deficiency increases the risk of severe neonatal jaundice, alpha-1-antitrypsin deficiency contributes to risk of early-onset liver disease and chronic lung disease in adult life. Many other common polymorphisms are genetic risk factors for common diseases of adult life. For example the common E4 polymorphism of the *APOE* gene is associated with increased risk of coronary heart disease, and the common C282Y allele in the *HFE* gene is associated with risk of haemochromatosis.

Disorders due to genetic risk factors

Disorders caused by the interaction of gene variants with weak effects on health with each other and with environmental factors. Rhesus negativity, G6PD deficiency and alpha plus thalassaemia are included in the Global Database because they are well-understood examples of genetic risk factors for early-onset congenital disorders.

Genetic polymorphism

"The occurrence of two or more alleles for a given locus in a population, where at least two alleles appear with frequencies of more than 1 percent" (Bodmer and Cavalli-Sforza 1976).

Allele / Allele frequency

Carrier / heterozygote

A heterozygote is an individual in whom the two copies of a given gene differ. In a medical context the term is usually used for an individual who has one normal copy of a given gene, and one copy that can potentially cause a genetic disorder.

Since only a minority of health professionals have a clear understanding of the specialist term *heterozygous*, we propose replacing it with the term "carrier" for communicating with a Community Genetic audience. With this usage-

- Carriers of dominant disorders are at high risk of developing the disorder themselves at some point in life, and have a 50% reproductive risk (i.e. each child has a 50% risk of inheriting the responsible gene variant).
- Carriers of recessive disorders have no personal risk of developing the disorders themselves. They have *potential* reproductive risk which only becomes an *actual*

reproductive risk if they have children with a partner who carries the same recessive disorder. They then have a 25% reproductive risk (i.e. each child has a 25% risk of developing the disease). Carriers of recessive disorders may be called *healthy carriers*, to emphasise that the carrier state does not predispose to any disorder.

- Carriers of X-linked disorders have a 25% reproductive risk (i.e. each male child has a 50% risk of inheriting an X chromosome that carries a gene for the disorder and developing the disease). A proportion of female carriers of X-linked disorders may also develop the disorder (with varying degrees of severity) as a result of unequal X-chromosome inactivation.

Carrier prevalence

The proportion of a population who are carriers of a specific single gene disorder.

Gene variant

Term used to describe a difference from the commonest DNA sequence of a gene. The commonest sequence may be called the *canonical* sequence.

Genetic polymorphism

When a variant affects more than 1% of genes it is viewed as a common variant and is called a *genetic polymorphism*. Most genetic polymorphisms are harmless or have weak effects on health. However polymorphisms that can cause disease but have a selective advantage, such as haemoglobin S, can reach high prevalence.

Balanced polymorphism

The situation where the frequency of a gene that gives a selective advantage but can also cause disease, stabilises because advantage and disadvantage are balanced. The best-known examples are haemoglobin disorders and G6PD deficiency, in malaria endemic areas.

Genetic fitness

Ability of an individual or group to pass their genes on to subsequent generations, by comparison with the population norm. This specialist term has strong negative connotations for some populations. The equivalent and more transparent term *reproductive success* is therefore used in the Global Database.

Reproductive success

Ability of an individual or couple to have descendants, when compared with the population norm. This term may be used as equivalent to genetic fitness. The term descendants includes children and grandchildren. A couple at risk for a genetic disorder may have the same number of children as others, but if those with the genetic disorder are unable to reproduce, the couple's ultimate reproductive success is reduced. Therefore the true measure of an individual's genetic fitness is their ability to transmit their genes to grandchildren and subsequent generations.

Reproductive disadvantage

Anything that interferes with an individual or couple's genetic fitness.

Consanguinity

The dictionary definition is "related by blood". Since this term applies for any blood relative it should be qualified when applied to the relationship between a couple.

Inbreeding

When used for human beings this is a highly pejorative term that should be avoided. It can usually be replaced by more neutral and precise terms such as consanguineous marriage or parental consanguinity.

Consanguineous marriage /union

A marriage between a individuals who are blood relatives. In medical genetics the term applies for a couple who are related as second cousins or closer. Strictly, the relevant relationship is a consanguineous *union* because not all parents are married. However most observational data actually applies for consanguineous marriage because surveys usually enquire into marriage relationships, and in many relevant populations marriage is virtually universal. In common parlance, consanguineous marriage is often called cousin marriage.

Parental consanguinity

In community genetics the main interest is in the implications for offspring of consanguineous parents, i.e. in the implications of parental consanguinity. This term is used as far as possible in the Global Database.

Coefficient of consanguinity (Coefficient of inbreeding)

A specialist term used for quantifying the genetic implications of parental consanguinity in terms of the additional proportion of gene pairs that are identical by descent (*F*). In the original specialist literature it was called the coefficient of *inbreeding*. However the term "inbreeding" is highly pejorative in popular usage and should be avoided with non-specialist audiences – indeed with any audience, since the borderline between specialists and the public is increasingly porous.

Interventions/prevention

Prevention

The word prevention is derived from the Latin *praevenire*, meaning to arrive first or beforehand, and applies for any intervention undertaken to avoid any specified event. However it is a very weighted and potentially contentious term in the context of Community Genetics. The problem is that prevention is a main aim for public health, and public health professionals include termination of pregnancy for fetal impairment as a form of prevention. But the abortion issue is so highly politicised in some settings that it can be desirable (or even necessary) to preclude discussion to avoid side-tracking. In this situation other euphemistic terms must be found, e.g. avoidance (of birth) or secondary prevention (see below). For this reason the term prevention is used as little as possible in the Global Database. Since it depends on intervention, it is replaced when possible by specifying the timing of the relevant intervention – before or during pregnancy or after birth.

Prevention of congenital disorders

Interventions for congenital disorders are intended to prevent associated death and disability. Specialist publications often describe three levels of prevention: (1) primary prevention, when a disorder is stopped from arising in the first place (e.g. maternal immunisation against rubella, anti-D for rhesus negative mothers, folic acid food fortification); (2) Secondary prevention: an affected fetus is prevented from reaching birth – a euphemism for termination of pregnancy; and (3) Tertiary prevention: an existing disorder is prevented from causing clinical problems (e.g. treatment of congenital hypothyroidism, cure of a congenital malformation by paediatric surgery). However, when the terms primary, secondary and tertiary prevention are used the general reader usually has to pause to check their meaning[23]. Therefore in the Global Database interventions are described according to their timing in relation to pregnancy.

- *Interventions before pregnancy*. This term covers pre-conception interventions that prevent disorders arising in the first place (e.g. anti-D, folic acid food fortification,

[23] Also, it can be hard to place some interventions in the hierarchy. For example, preventing virilisation of a female fetus with congenital adrenal hyperplasia, by treating the mother with dexamethasone throughout pregnancy - ?primary or secondary prevention.

genetic risk identification with information and counselling, polar body-based pre-pregnancy genetic diagnosis): it also includes intervention between conception and implantation (genetic diagnosis based on blastomere sampling).

- *Interventions during pregnancy*. This term covers identification of increased risk of congenital disorder with information and counselling, and prenatal diagnosis with or without the option of termination of an affected pregnancy. Benefits of prenatal diagnosis include informed choice of pregnancy outcome for the parents, intra-uterine treatment when this is possible, optimal neonatal care for an affected infant, and the option of termination of pregnancy if the fetus has a severe disorder (when this is legal).
- *Early diagnosis and care*. Optimal care often depends on early diagnosis. Early diagnosis includes prenatal diagnosis, neonatal diagnosis by physical examination or other investigation, and clinical paediatric diagnosis by trained professionals.

Birth outcomes

Miscarriage

The definition of miscarriage depends on the country definition of stillbirth, and this is highly variable. In the Global Database the term miscarriage is used for fetal loss before 20 weeks of pregnancy (measured from the last menstrual period).

Birth

This term covers all pregnancy outcomes after 20 weeks' gestation (measured from the last menstrual period). However, some pregnancies terminated for fetal impairment would have ended in miscarriage before 20 weeks. It may therefore be necessary to adjust terminations of pregnancy reported by congenital anomaly registries for estimated losses before 20 weeks, before including them in total births.

Stillbirth

The definition of stillbirth ranges by country from pregnancy loss after 20 weeks to loss after 28 weeks' gestation (measured from the last menstrual period), and weight is also usually taken into account. This naturally leads to difficulties in obtaining reliable data, and in comparing rates between countries and over time.

Fetal death

EUROCAT defines fetal death as death in utero after 20 weeks from the last menstrual period. In EUROCAT, and hence in the Global Database, fetal death is used as an indicator of prevalence of stillbirth. In theory this use might inflate stillbirth estimates (e.g. the WHO definition of stillbirth for global use is death in utero after 28 weeks' gestation). However there is good evidence that the prevalence of fetal death due to congenital disorders is under-estimated in many settings. Therefore it is reasonable to use observed fetal death rates as an indicator of stillbirth rates, in the absence of other reliable data.

Abortion

This is an ambiguous term that may be used both for miscarriage and for medically-induced abortion. Abortion is a highly politicised topic. Therefore the term abortion is best avoided when the aim is to give an objective description of birth outcomes.

Medically-induced abortion

The United Nations report on legality of medical abortion includes seven indications for medical abortion: (1) to save the life of the woman; (2) to preserve physical health; (3) to preserve mental health; (4) rape or incest; (5) *fetal impairment*; (6) economic or social reasons; (7) available on request.

Abortion for fetal impairment is included in the Global Database, under the heading termination of pregnancy (TOP) for fetal impairment.

Termination of pregnancy for fetal impairment

EUROCAT uses the term “termination of pregnancy for fetal anomaly” (TOPFA). However this term might be understood as applying only for congenital anomalies. The term used in the Global Database is termination of pregnancy (TOP) for fetal impairment, because the term impairment covers all severe congenital disorders and is consistent with UN usage.

Termination of pregnancy for fetal impairment is sometimes (often) counted as a solution to the problem presented by a congenital disorder. However in reality termination of a wanted pregnancy is a heavy cost for parents and so for societies. In the Global Database termination of pregnancy for fetal impairment it is included with fetal death, premature death and life-long disability, as a cost of congenital disorders.

Measures of frequency

Ascertainment

The proportion of actual cases that are recorded. It corresponds to sensitivity (true positive rate), defined as the proportion of actual positive cases correctly identified.

Incidence

The frequency with which new cases of a disorder arise. For public health purposes incidence is often expressed as new cases per 100,000 population per year. However the incidence of congenital disorders is best described in terms of birth prevalence, i.e. affected births/1,000 births (live births, or total births).

Prevalence

A measure of the number of cases of a disorder present in a given population at a given time, e.g. cases/100,000 population. Because of high early mortality, the birth prevalence of congenital disorders (rate/1,000 births) is far higher than their population prevalence (rate/1,000, 10,000 or 100,000 total population). When effective cure is possible, the population prevalence rises at a rate proportional to access to care, until it stabilises at the same level as birth prevalence. This equalisation can occur at 80 years from the start of effective intervention, at the earliest.

Birth prevalence

Throughout this series the term “birth prevalence” is used in place of “incidence” to describe the frequency of new cases as they present to health services. Strictly, incidence applies for the frequency with which new cases arise: many congenital disorders that arise at or soon after conception miscarry leading to wide differences between true incidence and frequency at birth. Therefore when the aim is to assess service needs, prevalence at birth is taken for practical purposes as equivalent to incidence. The distinction is not only theoretical: it matters practically – e.g. the difference between prevalence in the second trimester of pregnancy and at term must be taken into account when calculating the impact of prenatal diagnosis on the birth prevalence of congenital disorders.

- In this series birth prevalence is usually expressed in terms of affected births per 1,000 *live births*, because World Population Prospects (WPP) data provide the denominator, and in WPP the term “births” applies only for live births.
- In most congenital anomaly registries, including EUROCAT, birth prevalence is usually expressed in terms of affected births per 10,000 *total births*. (For Rare Diseases Orphanet uses cases/100,000).

Baseline birth prevalence (potential birth prevalence)

The birth prevalence that would obtain in the absence of any intervention. In congenital anomaly registries birth prevalence is usually expressed as rate/10,000 or /1,000 *total births* (stillbirths and live births). This is because: (a) congenital disorders make an important contribution to stillbirths; and (b) reliable data on stillbirth rates are available in most settings with congenital anomaly registries. However, at a global level, birth prevalence is usually expressed as rate/1,000 *live births*. This is because the most reliable and consistent source of global demographic data (UN World Population Prospects, WPP) only publishes estimates for live births (due to the difficulty of collecting reliable stillbirth data in many lower-income settings.) This difference leads to modest under-estimation when actual annual affected births are calculated by applying rates from congenital anomaly registries to WPP birth data.

Baseline birth prevalence provides the starting-point for assessing service need and the impact of different interventions.

Actual birth prevalence

Actual births /1,000 live births, allowing for the effects of interventions before or during pregnancy. (The denominator is live births because of the use of WPP birth data.)

Total birth prevalence

Includes all outcomes of affected pregnancies after 20 weeks' gestation (termination of pregnancy, fetal death/stillbirth, live birth). Expressed as total affected births /1,000 live births.

Live birth prevalence

Affected live births /1,000 live births

Reference rate

A rate that can be used as a yardstick for comparisons between countries or over time (e.g. baseline birth prevalence = reference rate for congenital disorders).

Live birth outcomes

Effective cure, e.g. for congenital malformations corrected by paediatric surgery. It does not mean complete correction with no residual problems. Rather it means that the problem has been sufficiently corrected to allow affected individuals to live their lives free from continuing medical care, and to achieve life goals such as independent living, finding a partner, reproductive success, even with some persisting problems.

Severe disability. Disability likely to cause premature death and/or prevent independent living and attainment of other life goals.

Mild/moderate disability. Disability that does not usually lead to premature death, may allow independent living, but may diminish reproductive success.

Residual disability. Disability that persists despite best possible care. May be severe, e.g. Down syndrome or spina bifida, or mild/moderate, e.g. some cases of oro-facial clefts.

Well on treatment. The condition of people born with a congenital disorder who are able to lead an effectively normal life including reproductive success, providing they have ongoing treatment (e.g. treated congenital hypothyroidism, phenylketonuria (PKU), thalassaemia major).

Demography

Level of economic development

The terms comparing developed/developing or industrialised/industrialising etc. are outdated. The World Bank classification of high, middle and low income countries is currently

used by the Global Burden of Disease study. In the Global Database the key distinction is between high income countries capable of providing optimal care equitably to their population, and countries that have not yet reached this level of economic development. Non-high income countries are often collectively described as "low and middle income countries" (LMIC). The collective term used in the Global Database is “lower-income countries (or settings)” because: (a) the crucial difference is between high income countries and the rest; and (b) it is desirable to avoid cumbersome usages and abbreviations. However our principal indicator of level of economic development is estimated access to services, based on infant mortality. That is, we really use a continuous rather than a stepped indicator.

Ethnic group

Ethnic minority. A population group that is distinguished genetically or culturally from the majority population of a country.

Sex ratio

The relationship between numbers of males and females in a group, usually expressed as males/females. Sex ratio at birth is similar worldwide in the absence of prenatal sex selection. When used in relation to population age distribution it gives a measure of excess of one sex or the other in any age group, and so may cast light on the history of the population.

Sex ratio at birth. The usual (male/female) sex ratio at birth is 1.05 +/- 0.01 (51.2% males, 48.8% females) with little geographical or ethnic variation.

Total fertility rate (TFR) (final family size)

The total fertility rate (TFR) of a population is the average number of children that would be born to each woman over her lifetime if: (a) She were to experience the exact current age-specific fertility rates through her lifetime; and (b) She were to survive from birth through the end of her reproductive life. It is obtained by summing the single-year age-specific rates at a given time. The estimate is for total births per woman, including stillbirths and live births.

TFR is used in the Global Database in estimates for disorders whose prevalence is related to birth number (e.g. rhesus haemolytic disease of the newborn), and in estimates of the potential maximum effect of genetic risk information on reproductive behaviour.

World Population Prospects (WPP) annual births

WPP estimates for births apply for live births only.

Reference region

A region chosen for comparison with other countries or regions because it demonstrates the maximum potential effect of available interventions. Data for this region can therefore be used as a yardstick for assessing the extent to which interventions are implemented in other regions, and for projecting the likely effects of future choices concerning available interventions at regional and global levels. Western Europe is chosen as the reference region for WHO regions.

Survival and mortality

Causes of death[24]

“In 1967, the Twentieth World Health Assembly defined the causes of death to be entered on the medical certificate of cause of death as “all those diseases, morbid conditions or injuries

[24] From Volume 2: Instruction manual, page 31. *(4. Rules and guidelines for mortality and morbidity coding*.) in World Health Organization. (2004). International statistical classification of diseases and related health problems. Geneva, World Health Organization. www.who.int

which either resulted in or contributed to death and the circumstances of the accident or violence which produced any such injuries". ---. When only one cause of death is recorded, this cause is selected for tabulation. When more than one cause of death is recorded, selection should be made in accordance with -- the concept of the underlying cause of death."

Underlying cause of death

"It was agreed by the Sixth Decennial International Revision Conference that the cause of death for primary tabulation should be designated the underlying cause of death. --- For this purpose, the underlying cause has been defined as: "(a) the disease or injury which initiated the train of morbid events leading directly to death; or (b) the circumstances of the accident or violence which produced the fatal injury".

Two examples: The sequence when a child with untreated Down syndrome dies may be: (a) pneumonia, due to (b) congenital heart disease, due to (c) Down syndrome: the underlying cause of death is Down syndrome. When a child with sickle cell disease dies in rural Africa the sequence may be: (a) infection, due to (b) functional asplenia, due to (c) sickle cell disorder: the underlying cause of death is sickle cell disorder.

Survival

For congenital disorders, the proportion of affected individuals born and still alive at given age intervals (usually 5-year intervals). Visually presented as a survival curve. In the Global Database, survival curves with optimal care and in the absence of care are needed for each disorder group. Availability of a full survival curve permits calculation of mean life expectancy (mean age at death) and so of years of life lost or lived with disability.

Prospective survival curve

A survival curve that describes the anticipated survival of affected individuals born today, assuming no new treatments become available. Survival curves with optimal care, based on the most recent available data, are in fact prospective survival curves.

Retrospective survival curve

A survival curve showing estimated survival of people living at a given time by age group, looking back over the previous 80 years. Retrospective survival curves take account of the history of the introduction of new therapeutic interventions. For example, routine closure of all open spina bifida only became policy in the early 1970s. Therefore although long-term survival is now expected for 70% of people with spina bifida, the retrospective survival curve predicts that in 2010 there would be relatively few survivors with spina bifida over 45 years old.

Mortality

The proportion of affected individuals who have died by given age intervals. The converse of survival.

Early mortality

Neonatal, infant, under-5 deaths/1,000 births.

Attributable mortality

The proportion of affected individuals who have died due to their diagnosis, rather than from any other cause. In calculating mortality attributable to congenital disorders, the relevant proportion of affected individuals who may have died from other causes before they would have died due to their condition, is subtracted from deaths calculated using survival curves.

Optimal care

In principle, optimal care should mean care including all the interventions available at the relevant time. In the Global Database it means the level of care typically available when infant mortality is 10/1,000 or lower.

No-care situation

A situation in which there is no access to health services of any kind, even basic primary care. (The baseline condition for human populations.)

Mean age at death

This term can be ambiguous because it may be used in two ways: (a) the mean age of death of all individuals with a given disorder; or (b) the mean age of recorded deaths. Czeizel used it in the second sense, so that in his data only 30% of Down syndrome cases died by the age of 20 but mean age at death was only 2.5 years. The sense in which the term is used must be clearly defined. In the Global Database, to avoid confusion and use a more optimistic tone, the equivalent term *mean life expectancy* is used.

Mean life expectancy

Mean life expectancy of all individuals with a given disorder. Equivalent to mean age at death for all individuals born with the disorder.

Access to care

As used in the Global Database, access to care means access to the typical range of services available when infant mortality is 10/1,000 or lower. Access to care is estimated using a formula based on infant mortality, taken as the single simplest indicator of level of health care development.

Specialist services

Costs and benefits

Unfavourable outcome / Favourable outcome

Costs / Benefits

To include discussion of years of life lost etc., and expression of costs and benefits in terms of rates per individual in the relevant birth cohort.

The “normal range” – a point for discussion in the context of the effect of vitamin supplementation on neural tube defects, and of alpha and beta thalassaemia on red cell indices.

Article 2: Core methods for estimates to five years of age

Abstract

This article specifies the congenital disorder groups included in the Modell Global Database of Congenital Disorders, and describes methods used to obtain country-specific epidemiological estimates from birth to five years of age.

The estimates are based on data from the following sources. (1) Country-specific estimates of birth prevalence are available for neural tube defects, oro-facial clefts, haemoglobin disorders, parental consanguinity, rhesus negativity and G6PD deficiency. (2) Birth prevalences and birth outcomes for congenital anomalies are available from "umbrella" registries of congenital anomalies (EUROCAT and ICBDSR); (3) Country specific demographic estimates are from UN World Population Prospects; (4) disorder-specific survival data obtained from the literature, supplemented by expert opinion.

Data from these sources are processed to create the following sets of country-specific inputs. (1) baseline birth prevalence (i.e. prevalence that would obtain in the absence of any intervention); (2) effects of pre-pregnancy interventions and termination of pregnancy on birth prevalence; (3) disorder-specific survival and disability (a) in a baseline no-care situation and (b) with optimal care.

Country-specific estimates of actual annual affected births, birth outcomes and survival to age five are then obtained by relating rates for birth prevalence and outcomes in the absence of care and with optimal care, to the estimated proportion of each population with access to optimal care. In the absence of a readily-available global source of information on access to optimal care, we use a method based on infant mortality rate.

We emphasise the central importance of baseline birth prevalence for all further calculations. (a) The evidence base for these estimates is particularly strong. (b) Baseline birth prevalence provides a quantitative envelope which must be filled by the sum of all outcomes.

The method is illustrated by charting selected outcomes by WHO region. Tables and charts also includes estimates for Western Europe, as a region which broadly represent outcomes with optimal care.

Calculations for 2010-14 indicate that current interventions, when fully deployed at the population level, can reduce pathological outcomes by over 60%, and under-5 deaths by around 80%. Currently, congenital disorders are estimated to cause over 20% of global under-five deaths, while in high income settings where general under-5 mortality is very low they may account for around 70% of under-5 deaths.

Introduction

A full description of the general method used in building the Global Database is unavoidably lengthy, and so is presented in two parts. This article describes the methods used for calculating outcomes up to at five years of age, while the next describes methods used for calculating long-term outcomes. The articles also include summaries of selected outputs by WHO Region.

The five-year break-point is chosen (a) because most deaths due to early-onset congenital disorders occur in the first few years of life; (b) reliable survival data is available up to five years of age for most of the disorders included; (c) under-5 mortality was the key indicator of access to appropriate services for the fourth UN Millennium Development Goal (MDG4), and (d) the calculations used for estimating long-term outcomes are more complex and results are more tentative.

Scope - conditions included

The Global Database provides country estimates of birth prevalence, mortality and disability for the 32 clinical diagnostic groups listed in Table 2.1. The table also indicates the principal sources for the birth prevalences currently used in the database, and the intermediate groupings used to "bundle" data for different purposes.

- The *chromosomal disorder* group includes all disorders that cause serious disability for the affected person[25].
- The *congenital malformation group* includes the ICD 10 system groups used in most congenital anomaly registries.
- The *additional conditions* group accommodates disorders that would be classed as congenital by paediatricians but are not included in congenital anomaly registries because either they are placed elsewhere in ICD 10, or cause functional rather than structural abnormality, or have uncertain status. At present only three examples are included as "place-holders" for this group.

Two groups of *genetic disorders* are included, but there is no sharp boundary between them.

- *Single gene disorders* are caused by DNA variants with strong effect and so follow Mendelian inheritance patterns (dominant, X-linked, recessive). Most individuals with the relevant variant (or combination of variants) develop the disorder. At present, only disorders that present before 20 years of age are included.
- *Disorders due to genetic risk factors* are caused by interaction of (often very common) DNA variants with other genetic and environmental factors[26]. The Global Database includes two early-onset examples (rhesus haemolytic disease of the newborn and neonatal jaundice due to G6PD deficiency) because (a) the underlying mechanisms are exceptionally well understood, and (b) they are potentially lethal but can be effectively prevented and/or treated.

[25] Chromosomal anomalies whose only effect is to increase reproductive risk (e.g. balanced structural rearrangements) are not currently included.

[26] This group may also be called "multifactorial disorders". However this broad term is not used in the Global Database because (a) it includes common disorders of adult life where gene/environment interaction is involved and (b) it is often mistakenly understood to mean that all cases have a genetic component. In fact most "multifactorial disorders" include a relatively small group of single gene disorders, some with both genetic and environmental causes, and some with purely environmental causes.

Table 2.1. Groups of early-onset constitutional congenital disorders included in the Global Database, with principal sources of birth prevalence data

Major group	Intermediate bundle	Diagnostic group	Principal sources for reference baseline birth prevalence rates
Chromosomal disorders	Severe autosomal disorders	Down syndrome (+21)	Hook and Hamerton (1977) Morris, Mutton *et al.* (2002); calculation based on maternal age
		Other trisomies (+13, +18)	
		Other autosomal	Wellesley, Dolk *et al.* (2012)
	Sex chromosome disorders	Turner syndrome (XO)	EUROCAT data
		Klinefelter syndrome (XXY)	Visootsak and Graham (2006), Morris, Alberman *et al.* (2008)
Congenital malformations	Neural tube defects	Anencephaly	Elwood, Little *et al.* (1992) Systematic review 2010. Literature. Personal communications.
		Spina bifida & encephalocele	
	Oro-facial clefts	Cleft lip +/- cleft palate (CL(P) Cleft palate (CP)	Mossey and Little (2002) Kadir, Mossey *et al.* (2016)
	Congenital heart disease (CHD)	Very severe CHD Severe CHD	EUROCAT (2009), Literature
	Other malformations: potentially very severe	CNS not neural tube defect Eye Ear, face, neck Respiratory system Digestive system Abdominal wall defects Urinary system Multiple malformations	E**U**ROCAT data
	Other malformations: usually less severe	Genital system	E**U**ROCAT data
		Limb	
	Additional conditions	Congenital hypothyroidism[1] Prem-assoc. persistent PDA	Modell and Modell (1992) EUROCAT data
		Pyloric stenosis	Pedersen, Garne *et al.* (2008) Modell and Modell (1992)
Single gene disorders	Rare single gene disorders	Dominant X-linked Rare recessives [2]	Classical studies (see Table 2.8 below)
	Consanguinity-associated disorders	Consanguinity-associated disorders	Bundey and Alam (1993) Bittles and Neel (1994)
	Haemoglobin disorders	Sickle cell disorders Thalassaemias	Modell and Darlison (2008)
Genetic risk factors	Rhesus haemolytic disease		Mourant, Kopeć *et al.* (1976) Bhutani, Zipursky *et al.* (2013)
	G6PD deficiency (G6PDd) neonatal jaundice (NNJ)		WHO 1985c, Howes, Piel *et al.* (2012)

1. *Hypothyroidism due to thyroid agenesis or dysgenesis. Hypothyroidism due to iodine deficiency is excluded.*
2. *Rare recessives = recessive disorders that would occur in the absence of parental consanguinity.*

Conditions not included

A comprehensive database of congenital disorders would include all conditions regardless of cause or age at onset. However the following groups are not currently included.

1. Environmental congenital disorders, for the reasons given above.

2. Non-genetic congenital disorders with functional rather than anatomical effects that are not included in congenital anomaly registries, e.g. cerebral palsy with intra-uterine onset[27].
3. Later-onset constitutional congenital disorders such as family cancer syndromes, genetically-determined neurodegenerative disorders, or cardiac disease due to bicuspid aortic valve.
4. Disorders due to genetic risk factors other than rhesus negativity, G6PD deficiency or alpha plus thalassaemia.

If, in the future, the concept of a Global Database of Congenital Disorders gains wider support, of these disorder groups may be progressively added.

Bundling disorder groups for presentation

All calculations in the Global Database are made separately for the 32 disorder groups in Table 2.1. However for clarity in presentation they must be aggregated into fewer, meaningful groups. There are relatively small inter-country differences in baseline birth prevalence of the first three groups - chromosomal disorders, congenital malformations and rare single gene disorders, but there are wide inter-country differences in the birth prevalence of consanguinity-associated disorders, haemoglobin disorders, rhesus haemolytic disease and G6PD deficiency. Table 2.2 shows the seven resulting "main disorder groups" and for each group the range of baseline birth prevalence and estimated under-5 mortality with no care.

Table 2.2. Main groups of congenital disorder as used in this report.

Main disorder group	Births /1,000		World average		Estimated % under-5 death if no care
	Min	Max	Births /1,000	% of total	
Chromosomal disorders	3.4	5.8	4.0	10.1	57-65
Congenital malformations	20.7	30.9	21.2	53.4	52-63
Rare single gene disorders	3.6		4.5	11.4	11.4
Consanguinity-associated	0	21.6	4.3	10.8	72
Haemoglobin disorders	0	25.5	3.2	8.2	5-95
Rhesus haemolytic disease	0.05	6.4	2.2	5.6	50-82
G6PDd neonatal jaundice	0	2.45	0.2	0.5	77

Desired outputs

The first step is to define the desired outputs, since they determine the inputs that are needed. To meet the information needs of policy-makers, the Global Database can generate the following outputs for each disorder group.

- Affected birth prevalence in the absence of any intervention (baseline birth prevalence). This is the starting point for quantifying the scale of the problem.
- Outcomes in the absence of any intervention - stillbirth, death, disability at 5 years of age[28] and lifetime. These are starting points for assessing the effects of interventions.
- Available interventions. Table 2.3 lists available interventions before pregnancy, during pregnancy or after birth, and their potential benefits, and shows those that are quantifiable in the Global Database.

[27] Neurological damage leading to cerebral palsy may occur in utero, at birth, or later e.g. due to cerebral malaria. In high income settings, the first predominates and birth prevalence is approximately known.
[28] Five years of age is chosen as a critical "end-point" because the present database includes only early-onset disorders, which have their greatest impact in terms of mortality within the first five years. In addition, under-5 mortality was the chosen outcome point for Millennium Development Goal 4.

Table 2.3. Interventions that can affect the birth prevalence and outcomes of congenital disorders[29]

Timing of intervention	Intervention	Possible benefit	Quantifiable in database
Before pregnancy	Anti-D for rhesus negative mothers	Conversion of potential affected pregnancy to unaffected pregnancy	Yes
	Multi-vitamin supplementation.		No
	Folic acid food fortification		Yes
	Identification of genetic risk, information, genetic counselling	Informed reproductive choice	Yes
During pregnancy	Identification of increased risk, information, counselling. Prenatal diagnosis	Informed choice of intervention Intra-uterine treatment Option of termination of pregnancy Appropriate, timely neonatal care	Yes No Yes No
After birth	Early diagnosis and care	Effective cure, or well on treatment Improved survival Reduced disability	Yes Yes Partly

- Effect of interventions before birth. Actual birth outcomes (termination of pregnancy, stillbirth, live birth)
- Effect of interventions after birth. Actual outcomes to age 5 (neonatal, infant, under-5 mortality, disability, cure).
- Current number and age distribution of living affected individuals, untreated or treated, in the population.
- Potential future effects of present policies, and of possible changes in policies, on numbers of affected individuals and outcomes.

Policy-makers also seek an assessment of costs and benefits. It is not possible to give an assessment of financial costs, as these vary widely depending on country. In addition, many of the human costs associated with congenital disorders are difficult to quantify. Nevertheless, the above outputs go a long way to providing a basis for formal economic analysis at the country level.

Inputs required

Evidence-based estimates for most of the desired outputs can be generated from the following inputs.

For every country

- Basic demographic data. Most of the necessary date is available from the UN World Population Prospects (WPP) (http://esa.un.org/unpd/wpp). WPP provides country estimates from 1950 to 2015, with projections to 2100 using different assumptions. Rates for stillbirths, neonatal mortality and parental consanguinity are obtained from other sources (see *Article 4: Uses of demographic and geographic data*).
- Estimated access to services. This is calculated on the basis of infant mortality (see Article 5: Estimating access to services.)

For each disorder group

- Baseline birth prevalence (the prevalence that would apply in the absence of any intervention): total affected births, stillbirths, live births per 1,000 live births.
- Available interventions before pregnancy, during pregnancy, and after birth.
    - Historical evolution of each intervention over time.

[29] Obviously, these interventions form part of a comprehensive package including interventions for both environmentally- determined and constitutional congenital disorders.

- Effects of interventions in terms of the quantifiable benefits listed in Table 2.3.

- Survival of live-born affected individuals (a) in the absence of care and (b) with optimal care, by five-year intervals.
- Proportion of adult survivors expected to achieve universal life objectives such as living independently, building a family.

Demographic input data

Table 2.4 shows the range of demographic data used in the Global Database. Most are used in standard calculations for all disorder groups. The lower three rows show items used for specific purposes.

Table 2.4. Range of demographic data used in the Global Database, by topic

Type of data	Chromo-somal disorders	Congen-ital malform-ations	Haemo-globin disorders	Rare single gene	Consan-guinity-related	Rhesus haemo-lytic disease	G6PD defic NNJ
Population 1000s	•	•	•	•	•	•	•
Population age distribution	•	•	•	•	•	•	•
Annual births 1,000s	•	•	•	•	•	•	•
Stillbirth rate	•	•	•	•	•	•	•
Neonatal mortality	•	•	•	•	•	•	•
Infant mortality	•	•	•	•	•	•	•
Under 5 mortality	•	•	•	•	•	•	•
Average life expectancy (M & F)	•	•	•	•	•	•	•
Total fertility rate (TFR)			•	•		•	
% of mothers 35 plus	•						
Coefficient of consanguinity (F)			•		•	•	

Access to services is calculated from infant mortality, with adjustment for the effects of parental consanguinity and AIDS- related infant deaths, as described in Article 5: Estimating access to services*.*

UN World Population Prospects (2015 revision) provides reference data for most items. Other data sources are: stillbirths: Blencowe, Vos *et al.* (2013); neonatal mortality: www.childmortality.org, Cousens, Blencowe *et al.* (2011); coefficient of consanguinity: Bittles and Black (2010b), Bittles and Black (2010a), Bittles' *www.consang.net* and personal communications.

Aggregating country data for regional and global comparison

National policymakers are, of course, primarily interested in data for their own country. Detailed tabular country data is best published online to enable rapid access, and to allow for updating to reflect changes with time. For more general purposes and to aid comparisons and benchmarking, countries must be bundled into regions that are appropriate for the relevant audience. WPP 2015 bundles 233 UN countries/territories geographically into six continental regions and 24 sub-regions, but other organisations bundle them differently depending on their objectives (see *Article 4: Uses of demographic and geographic data*). The WHO bundles them administratively and pragmatically into six regions each served by a regional office - the African Region (AFR), American Region (AMR), Eastern Mediterranean Region (EMR), European Region (EUR), South East Asian Region (SEAR), and Western Pacific Region (WPR). The Global Burden of Disease (GBD) study[30] bundles them into seven super-regions and 21 sub-regions: GBD bundling has the advantage that it also takes account of income level, a key determinant of health service development.

[30] www.healthdata.org/gbd

Because this project is designed to support policy-making at the national level, facilitated by the relevant WHO Regional Office, it is appropriately illustrated using the WHO regions[31]. However their large size and the wide range of countries/territories covered by each region obscures important differences. To enable more fine-grained presentation of estimates we therefore created a set of provisional sub-regional country groups intended to reflect the approximate level of health services development, and so based on GBD sub-regions as far as possible.

Table 2.5 lists the countries/territories included in each WHO region and provisional sub-region generated in this way. Table 2.6 shows average annual births and infant mortality by WHO region and sub-region in 1990-94, and 2010-14, i.e. spanning the operational period of Millennium Development Goal 4 (MDG4) "to reduce by two-thirds, between 1990 and 2015, the under-five mortality rate".

Interventions are most fully deployed at the population level in high income settings, though local policies may limit e.g. folic acid food fortification or access to termination of pregnancy. Thus when a WHO region includes a high income sub-region this may be seen as a *local reference region* that demonstrates the potential effects of available interventions throughout that WHO region.

The use of reference populations

Western Europe is used as a *global reference region* because it includes a large population (currently 4.5 million births annually) in which available interventions (apart from folic acid food fortification) are near-equitably deployed at the population level, and their actual impact is recorded (e.g. by registries) or can be assessed by other means. Data for Western Europe can therefore be used to assess the maximum achievable effect (the "power") of the interventions when fully deployed, and results can be used to project the likely effects of future choices to deploy these interventions elsewhere.[32]

Other high income sub-regions that could be used as regional reference populations include: the North American and South America High Income regions for AMR, the Gulf States for EMR, and Asia Pacific High Income for WPR. However for these, most rates are calculated using the Database rather than directly observed as in Western Europe. There are no corresponding high income reference regions for AFR and SEAR.

For these reasons, observed rates for Western Europe are included for comparison in most charts and tables.

[31] In addition, the present project is supported by the WHO Office for the Eastern Mediterranean Region.

[32] This should not be taken to imply that all interventions should be deployed as in Western Europe – e.g. termination of pregnancy for fetal impairment is politically and socially accepted in most of Europe but this may not be the case elsewhere.

Table 2.5. Bundling of countries/territories by WHO Region, and the provisional sub-regions used for more fine-grained presentation of data from the Modell Global Database

WHO African Region (AFR)
North Africa. Algeria, Western Sahara.
Sub-Saharan Africa. Angola, Benin, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mayotte, Mozambique, Niger, Nigeria, Réunion, Rwanda, Saint Helena, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, South Sudan, Togo, Uganda, United Republic of Tanzania, Zambia.
Southern Africa. Botswana, Lesotho, Namibia, South Africa, Swaziland, Zimbabwe.

WHO American Region (AMR)
North America. Canada, Greenland, Saint Pierre and Miquelon, United States of America.
Caribbean. Anguilla, Antigua and Barbuda, Aruba, Bahamas, Barbados, Belize, Bermuda, British Virgin Islands, Caribbean Netherlands, Cayman Islands, Cuba, Curaçao, Dominica, Dominican Republic, French Guiana, Grenada, Guadeloupe, Guyana, Haiti, Jamaica, Martinique, Montserrat, Puerto Rico, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Sint Maarten (Dutch part), Suriname, Trinidad and Tobago, Turks and Caicos Islands, United States Virgin Islands.
Central America. Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Venezuela (Bolivarian Republic of).
South America. Bolivia (Plurinational State of), Brazil, Ecuador, Paraguay, Peru.
South America High Income. Argentina, Chile, Falkland Islands (Malvinas), Uruguay.

WHO Eastern Mediterranean Region (EMR)
Gulf States. Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates.
North Africa /Middle East. Egypt, Iran (Islamic Republic of), Iraq, Jordan, Lebanon, Libya, Morocco, State of Palestine, Sudan, Syrian Arab Republic, Tunisia, Yemen.
South Asia. Afghanistan, Pakistan.
East Africa. Djibouti, Somalia, South Sudan.

WHO European Region (EUR)
Western Europe. Andorra, Austria, Belgium, Channel Islands, Cyprus, Denmark, Faeroe Islands, Finland, France, Germany, Gibraltar, Greece, Holy See, Iceland, Ireland, Isle of Man, Israel, Italy, Liechtenstein, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Spain, Sweden, Switzerland, United Kingdom.
Central Europe. Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Montenegro, Poland, Romania, Serbia, Slovakia, Slovenia, TFYR Macedonia.
Eastern Europe. Belarus, Estonia, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine.
Middle East. Turkey.
Central Asia. Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan.

WHO South East Asian Region (SEAR)
South Asia. Bangladesh, Bhutan, India, Nepal.
Southeast Asia. Indonesia, Maldives, Myanmar, Sri Lanka, Thailand, Timor-Leste,
East Asia. Dem. People's Republic of Korea

WHO Western Pacific Region (WPR)
East Asia. China, Mongolia.
Southeast Asia. Cambodia, Lao People's Democratic Republic, Malaysia, Philippines, Viet Nam.
Asia Pacific High Income. Brunei Darussalam, China, Hong Kong SAR, China, Macao SAR, Japan, Other non-specified areas (Taiwan), Republic of Korea, Singapore.
Oceania. American Samoa, Cook Islands, Fiji, French Polynesia, Guam, Kiribati, Marshall Islands, Micronesia (Fed. States of), Nauru, New Caledonia, Niue, Northern Mariana Islands, Palau, Papua New Guinea, Samoa, Solomon Islands, Tokelau, Tonga, Tuvalu, Vanuatu, Wallis and Futuna Islands.
Australasia. Australia, New Zealand.

Table 2.6. WHO regions and proposed sub-regions, with average infant mortality and annual births, 1990-2014 (WPP 2015 revision)

WHO sub-region	Infant deaths /1,000 live births		Annual births	
	1990-94	2010-14	1990-94	2010-14
North Africa (Algeria, Western Sahara)	47.9	30.4	798	960
Sub-Saharan Africa	115.1	64.8	20,615	31,399
Southern Africa	52.6	42.1	1,664	1,871
AFR Total	108.3	62.6	23,077	34,230
North America	8.6	5.9	4,429	4,365
Caribbean	45.3	26.9	882	791
Central America	33.3	18.5	4,981	4,710
South America	46.6	21.7	4,908	4,414
South America High Income (Argentina, Chile)	22.9	12.2	1,058	1,039
AMR Total	30.6	15.8	16,257	15,319
Gulf region	28.2	12.7	759	913
EMR middle income	103	21.0	5,099	6,982
EMR low income	127.6	66.6	597	9,011
EMR Total	73.1	44.8	13,951	16,906
Western Europe	6.8	3.3	4,429	4,424
Central Europe	17.1	6.3	1,567	1,173
Eastern Europe	20.5	8.2	2,464	2,530
Middle East (Turkey)	56.2	12.6	1,381	1,304
Central Asia	63.6	33.4	1,822	1,865
EUR Total	25.8	10.7	11,662	11,296
South Asia	83	40.3	31,967	29,722
Southeast Asia	52.9	25.7	7,174	7,224
East Asia (North Korea)	42.1	22	436	358
SEAR Total	77.1	37.3	39,577	37,304
East Asia	40.5	11.7	22,699	16,938
Southeast Asia	38.5	21.6	5,118	4,941
Asia Pacific High Income	6.2	2.6	2,397	1,838
Oceania	58.7	41.9	227	279
Australasia	6.9	4	318	372
WPR Total	37.3	13.3	30,759	24,368
World	63	35.8	135,284	139,840

Note 1. Sub-regions for five of the WHO regions are based on GBD sub-regions. This was not possible for the EMR as the GBD uses a single North Africa/Middle East/Central Asia region (even though the countries included range from the Gulf States at one extreme of economic development to Somalia and Djibouti at the other). Therefore for the purposes of the Global Database EMR countries are bundled into four sub-regions based on infant mortality.

Note 2. Naming can be confusing when one GBD sub-region spans more than one WHO region, especially when only one or two countries are involved. In such cases the names of the countries concerned are also shown in the table. For the sake of clarity these country names are then used in relevant tables throughout this series.

Estimating access to services

Outcomes at the extremes – those in the absence of diagnosis and care, and with optimal care (i.e. when all interventions are fully and equitably available) - can be characterised for most groups of congenital disorders. In the highest income countries, average outcomes will be close to those for optimal care, while in the lowest income countries outcomes will be closer to those in the absence of care. However, the majority of countries lie somewhere between these two extremes. Estimates for these countries can be obtained by combining estimates for the two extremes in proportions that reflect an estimate of access to optimal services.

However no readily-accessible source for assessments of access to services exists. To fill this gap when estimating the global burden of neonatal morbidity the WHO Child Health Epidemiology Reference Group (CHERG) estimated access in relation to five neonatal mortality groups (Blencowe, Vos *et al.* 2013) and considered that neonatal mortality of less than 6/1,000 (equivalent to an infant mortality of around 10/1,000) indicates that a population has near 100% access to optimal care. This is consistent with an earlier WHO estimate that

infant mortality can only fall below 10/1,000 when services for congenital disorders are available (WHO 1985a). The term *optimal care* as used here therefore applies to the range of services typically available when infant mortality is 10/1,000 or lower.

Using the CHERG estimates as a starting-point, we developed an equation based on infant mortality for estimating the proportion of each population with access to optimal services (see *Article 5: Estimating access to services* for details).

Using the BETA.DIST function in Microsoft Excel the equation is:

Proportion with access = (1-BETADIST(LN(IMR-10),2.5,5.5,0,LN(1000)))

Figure 2.1 shows the proportion of the population of each WHO region estimated to have access to optimal care from 1950 to 2015, using this equation.

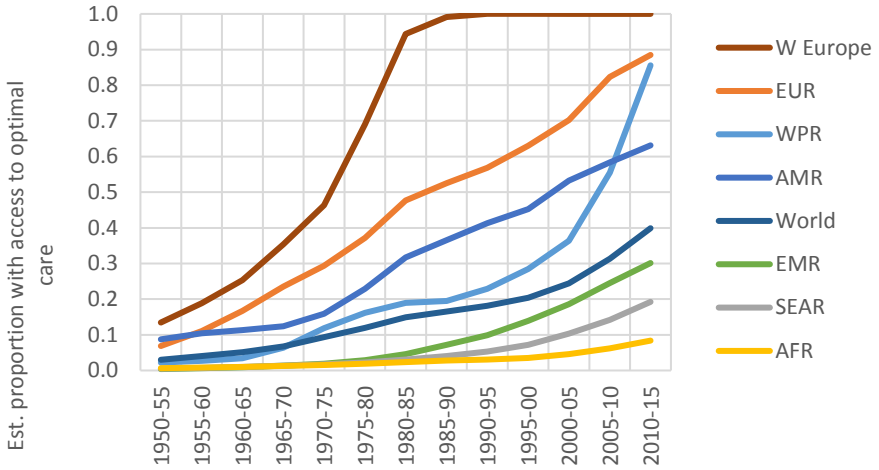

Figure 2.1. Chart showing increasing proportion of the population with access to optimal services by WHO region, 1950-2015, calculated from infant mortality using the equation described in *Article 5: Estimating access to services*. In the Western European reference region average infant mortality in 1950 was over 40/1,000. It fell below 10/1,000 in the 1980s, coinciding with the development of key services for care and prevention of congenital disorders, summarised in Table 2.11.

The estimate that the Western European population only obtained access to optimal services in the 1980s, which seems surprising at first sight, reflects the fact that infant mortality in the region was over 40/1,000 in 1950, and many services now considered routine were developed during the 1970s and 1980s (see Table 2.11).

Baseline birth prevalences

The level of a disorder in a population is usually described in terms of *incidence* (number of new cases arising in a defined time period) and *prevalence* (cases present in a given unit of population e.g. per thousand or per million). The true incidence of congenital disorders is the rate at which they arise - usually at or soon after conception. However so many affected embryos may fail to implant or miscarry that the true incidence is hard to establish and may bear little relationship to their prevalence at birth, the rate of greatest importance for health services. Therefore for practical purposes their *birth prevalence* is treated as their incidence, and expressed as affected births per /1,000 total births.

Baseline, or potential, birth prevalence is the prevalence that would apply in the absence of any intervention. It provides the foundation of the Global Database because it is the estimate with the strongest evidence base. Since it is relatively constant for any given population it also provides an “envelope” into which all outcomes must “fit”. For this reason the sources used to derive baseline birth prevalences must be considered in some detail. Baseline birth prevalence includes stillbirths and live births but excludes miscarriages.

Miscarriage

The definition of miscarriage depends on the definition of stillbirth, which differs widely by country (see below). To solve this problem EUROCAT reports numbers of "fetal deaths" defined as death in utero after 20 weeks' gestation[33]. By implication losses before 20 weeks' gestation are viewed as miscarriages. The Global Database follows this convention. It does not include miscarriage, and uses fetal death as a proxy for stillbirth.

Birth outcomes

Following the EUROCAT convention, all pregnancy outcomes after 20 weeks' gestation are counted as births.

Terminations of affected pregnancies

Since practitioners aim to achieve a definitive prenatal diagnosis as early in pregnancy as possible, many terminations for fetal impairment occur before 20 weeks' gestation, but some of these pregnancies would have miscarried spontaneously in the absence of intervention. Total terminations must therefore be adjusted using known rates for fetal loss in relation to gestational age. Only cases where the pregnancy would otherwise have continued past 20 weeks are included in the Global Database.

Fetal death and stillbirth

The legal definition of *stillbirth* ranges by country from death in utero after 20 weeks' gestation to death after 28 weeks' gestation, and may or may not also take account of weight. In addition, reporting varies with country, time and social attitudes. The ICD10 definition of stillbirth is death in utero after 22 completed weeks' gestation (WHO (2006), Stanton, Lawn *et al.* (2006)), but the current WHO definition is fetal death in the third trimester (≥1000 g birthweight or ≥28 completed weeks of gestation) (Cousens, Blencowe *et al.* 2011).

EUROCAT manages the inconsistent definition of stillbirth by reporting all in utero deaths after 20 weeks' gestation as "fetal deaths", and uses this figure as a proxy for stillbirth, e.g. in estimating perinatal mortality associated with congenital anomalies. This convention is followed in the Global Database, and the term "fetal death/stillbirth" is used to ensure clarity.

Live births

For most disorder groups, the birth prevalences of congenital anomalies used to calculate annual affected births etc. in the Global Database are total birth prevalences (i.e. include terminations of pregnancy and fetal deaths). In these cases live births are estimated by subtracting termination and fetal death rates from total affected births.

However the WPP birth data which provides the main denominator for calculating birth prevalence applies for live births only[34]. This leads to slight under-estimation of both total affected births and affected live-births.

Premature births

Though 7-8% of births are pre-term, 18% of congenital anomalies occur in pre-term infants. Honein, Kirby *et al.* (2009) found an average malformation rate of 80/1,000 among pre-term babies compared with 30/1,000 among term babies, the extent of association differing with degree of prematurity and malformation group (Table 2.7).

[33] See EUROCAT Guide 1.4 available at www.eurocat-network.eu

[34] This is not obvious on the WPP website, or in the associated glossary. However the UN Demographic Yearbook series (UNDY) specifies that births = live births: we assume this also applies for WPP birth data.

Table 2.7. Association of major malformation groups with prematurity in 8.88 million births: ranked in descending order of proportion of premature births (data from Honein, Kirby *et al.* (2009))

System affected	Live born affected	Affected /1,000 live births	% of births pre-term	Prevalence ratios[1]	
				Very pre-term (24 to 31 wk)	Moderately pre-term (32 to 36 wk)
Population rate			7.7		
Abdominal wall	3,076	0.46	43	7.7	9.2
Central Nervous System	16,215	2.40	34	16.2	4.3
Respiratory tract	10,722	1.58	26	11.5	2.9
Cardiovascular[2]	61,898	9.16	26	9.3	3.2
Gastrointestinal[3]	27,338	4.05	21	5.0	2.8
Eye, face, neck, ear	17,863	2.64	20	5.2	2.6
Genito-urinary	50,056	7.41	18	4.1	2.3
Musculo-skeletal	66,579	9.85	17	3.4	2.2
Skin	11,885	1.76	15	2.1	2.0
Orofacial	9,536	1.41	15	2.8	1.9

1. *The prevalence ratio is the prevalence in pre-term infants as a multiple of the rate in term infants.*
2. *Includes patent ductus arteriosus*
3. *Includes pyloric stenosis 1.59/1,000*

The causal relationship between congenital disorders and prematurity is unclear: some malformations may cause premature birth (e.g. CNS and lung malformations that affect formation or circulation of amniotic fluid), others may be caused by it (e.g. cardiac defects related to changing blood flow at birth). Congenital anomaly registries as a rule do not report on prematurity, except to exclude prematurity-related persistent patent ductus arteriosus. Therefore, because of lack of data, no allowance is currently made for this association in the Global Database.

Classical studies of birth prevalence

Extensive studies of the birth prevalence of congenital disorders were conducted in the aftermath of the second world war, in order to establish a baseline for assessing possible effects of exposure to atomic radiation, on the assumption that an increase in mutation rate would manifest as increased birth prevalence of affected children (United Nations. Scientific Committee on the Effects of Atomic Radiation. (1977), (1982) and (1986))[35]. Table 2.8 shows the most important of these classical studies and the disorder groups surveyed. Although the range of diagnoses included differed between studies, the rates observed were broadly consistent, and were generally considered to apply world-wide (Baird, Anderson *et al.* 1988).

These studies have the advantage that they predate the introduction of interventions that reduce affected birth prevalences (e.g. periconceptional vitamin supplementation, termination of pregnancy for fetal impairment), or increase detection rates (e.g. routine fetal anomaly scanning, sophisticated neonatal screening). The rates observed therefore represent uncomplicated baseline birth prevalences.

[35] The Hungarian registry enabled reassurance for the Hungarian population on after-effects of the Chernobyl disaster ().

Table 2.8. Classical studies of the birth prevalence of congenital disorders[1]

Source	Chromosomal disorders	Congenital malformations	Single gene disorders
Neel (1958)		+	
Stevenson (1959)	+	+	+
Stevenson, Johnston *et al.* (1966)		+	
Trimble and Doughty (1974)	+	+	+
Myrianthopoulos and Chung (1974)		+	
Carter (1977)			+
Ash, Vennart *et al.* (1977)	+	+	+
Hook and Hamerton (1977)	+		
Czeizel and Sankaranarayanan (1984)	+	+	
Baird, Anderson *et al.* (1988)	+	+	+

Note. All studies included only disorders that cause early death or life-long disability in the absence of intervention.

Concern about atomic radiation, proof of the effect of rubella infection during pregnancy, and the thalidomide disaster of the 1960s led to recognition of the need for ongoing surveillance of congenital anomalies, and ultimately to initiation of the International Clearing House for Birth Defect Surveillance and Research (ICBDSR, www.*icbdsr.*org) in 1974, and the linked European Surveillance of Congenital Anomalies (EUROCAT, *www.eurocat-network.eu*) network in 1979. These “umbrella registries” are a key source of reference data and have the outstanding advantage that in addition to reporting birth prevalences, most participating registries also record birth outcomes including termination of pregnancy for fetal impairment, fetal death/stillbirth, and live birth, and so enable the effect of prenatal diagnosis with the option of termination of pregnancy to be quantified.

Sources for rates used in the Global Database

Table 2.1 shows the sources for the total birth prevalences used in the Global Database. Table 2.10 shows rates for total affected births and fetal deaths/stillbirths. Sources for fetal death/stillbirth rates are: chromosomal disorders and congenital malformations, EUROCAT data adjusted for associations; multiple malformations, J Rankin, personal communication re Tennant, Pearce *et al.* (2010); consanguinity-related and recessive disorders, Bundey and Alam (1993) and Bittles and Black (2010b); Rhesus haemolytic disease, from the literature.

Avoiding double counting when categories overlap

To ensure scientific rigor, it is necessary that numbers be counted as accurately as possible, and to show how possible errors are avoided. The overlap between categories in Figure 1.1 in the introductory article indicates that there can be a risk of double counting.

Given the appropriate inputs, the precise outputs desired and the way in which they are calculated depend on the objective of the particular exercise. For example, the Born Healthy toolkit (Nacul, Stewart *et al.* (2014) and http://toolkit.bornhealthy.org) promotes assessment of service needs. For this purpose, the *number of all conditions* must be summed, that is, individuals who appear in overlapping categories must be counted more than once. Thus the need for paediatric cardiac surgery is assessed by summing all cases of congenital heart disease, whether isolated, associated with another type of malformation, or part of a chromosomal or genetic syndrome.

The objective of the present exercise is to estimate *numbers of individuals* with one or more congenital disorders, and outcomes *for those individuals* in terms of survival, disability, and mortality. The existence of overlapping categories therefore causes a serious risk of inflating estimates by double counting. There are two sources of risk, both associated with congenital malformations. (1) Congenital anomaly registries include all cases with a detectable malformation independent of cause, while the other three categories are based on cause, creating overlap between groups. (2) Most congenital anomaly registries report *numbers of*

malformations rather than numbers of affected individuals, in the process counting individuals with more than one type of malformation multiple times.

In the Global Database double counting is avoided as follows.

1. A *chromosomal disorder* usually represents a complex syndrome, often including malformations. Fortunately the umbrella registries distinguish between chromosomal-associated malformations and non-chromosomal malformations. Chromosomal-associated malformations are treated as part of the relevant chromosomal syndrome.
2. Malformations associated with *single gene disorders* (e.g. skeletal dysplasias) or other genetic syndromes, and consanguinity-associated congenital malformations[36] are included with single gene disorders.
3. The two *early-onset genetic risk factors* included (rhesus negativity and G6PD deficiency) do not overlap with other groups of constitutional congenital disorders.

These steps remove sub-groups of malformations, leaving a large group of *non-syndromic congenital malformations.* In order to obtain numbers of affected individuals, this group must be adjusted for double counting, i.e. it is necessary to distinguish individuals with *isolated congenital malformations* (affecting only one system) from those with *multiple malformations*. Table 2.7 shows that around 16% of non-syndromic malformations are associated, i.e. contribute to multiple malformations. It is particularly important to adjust for associations when assessing birth outcomes, because termination of pregnancy and fetal death are commonest in the multiple malformation group. Adjustment leads to the conclusion that (in Western Europe) 11% of malformations in live-borns are associated, compared with 37% in terminations and 44% in fetal deaths (Table 2.9). For details of the calculation see *Article 7: Congenital malformations: birth prevalence and birth outcomes*.

With this approach, *the number of individuals with a constitutional congenital disorder* is the sum of those with a chromosomal disorder, an isolated congenital malformation, multiple malformations, a single gene disorder, or a disorder due to the effect of an early-onset genetic risk factor.

Table 2.9. Non-syndromic congenital malformations: adjusting rates for double counting (based on average EUROCAT rates for 2005-09, for countries where termination of pregnancy is legal and reported

	Total /1,000	Birth Outcomes		
		Live births /1,000	Fetal deaths /1,000	TOPs /1,000
Non-syndromic ***malformations***	23.6	20.2	0.4	2.96
Individuals with 1 or more malformation	19.8	17.9	0.25	1.66
Difference /1,000	3.8	2.3	0.15	1.30
% difference	16.0	11.5	37.4	44.1
% isolated	**84**	**88.5**	**62.6**	**55.9**

Baseline birth prevalences used in the Global Database

Table 2.10 shows the global average baseline prevalences for 2010-14 generated by the Global Database. Rates are shown for total birth prevalence, fetal death/stillbirth[37] and live birth. The figures shown are global averages: actual input data differs by country. The table

[36] For discussion of malformations related to parental consanguinity, see *Article 11: Gene clustering and parental consanguinity*.

[37] Sources for fetal death/stillbirth rates are as follows. Chromosomal disorders and congenital malformations, EUROCAT data adjusted for associations. Multiple malformations, J Rankin, personal communication re Tennant et al. (2010). Consanguinity-associated and recessive disorders, Bundey, S. and H. Alam (1993). "A five-year prospective study of the health of children in different ethnic groups, with particular reference to the effect of inbreeding." Eur J Hum Genet **1**(3): 206-219. and Bittles, A. H. and M. L. Black (2010b). "The impact of consanguinity on neonatal and infant health." Early Hum Dev **86**(11): 737-741. Rhesus haemolytic disease, from the literature

indicates groups considered to have closely similar prevalence world-wide and those whose birth prevalence is known to differ by country.

The total global estimate for total affected births of isolated congenital disorders is 40/1,000. Figure 2.2 shows the relative contributions of the main disorder groups to this total.

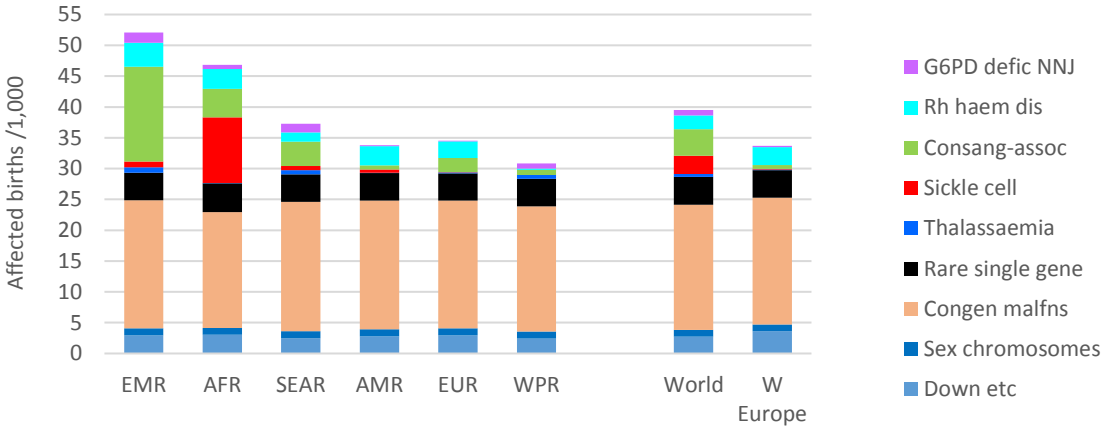

Figure 2.2. Baseline constitutional congenital disorders: total births /1,000, world by WHO Region, ranked in descending order of total baseline birth prevalence. Estimates for the Western European reference population are included. There is relatively little inter-regional variation for chromosomal disorders and congenital malformations (congenital anomalies). Inter-regional differences are mainly due to inter-country differences in baseline birth prevalence of genetically-determined disorders.

Table 2.10. Average global rates for baseline (potential) birth prevalences of the disorder groups included in the Global Database (2010-14)

Main group	Disorder group	Birth prevalence variable or constant	Estimated global average, 2010-14			
			Potential total births (SB & LB) /1,000	Potential fetal deaths /1,000	Potential live births /1,000	% fetal deaths
Chromosomal disorders	Down syndrome	Maternal age related	1.67	0.08	1.59	4.8
	Other trisomies (+13, +18)		0.69	0.37	0.31	54.7
	Other autosomal	Invariant	0.70	0.15	0.55	21.7
	Turner syndrome (XO)	Invariant	0.22	0.05	0.18	21.1
	Klinefelter syndrome (XXY)	Invariant	0.72	0.02	0.70	2.6
Isolated congenital malformations	Anencephaly	Country rate	1.03	0.51	0.51	50.0
	Spina bifida & encephalocele	Country rate	1.12	0.10	1.02	9.0
	Oro-facial clefts	Country rate	0.92	0.01	0.91	1.5
	Very severe CHD	Invariant	0.39	0.01	0.38	2.9
	Severe CHD	Invariant	2.94	0.02	2.92	0.7
	CNS not neural tube defect	Invariant	0.87	0.03	0.84	3.8
	Eye	Invariant	0.27	0.00	0.27	0.2
	Ear, face, neck	Invariant	0.27	0.00	0.27	1.3
	Respiratory system	Invariant	0.49	0.03	0.46	6.1
	Digestive system	Invariant	0.96	0.01	0.95	1.2
	Abdominal wall defects	Invariant	0.36	0.02	0.33	6.2
	Urinary system	Invariant	2.59	0.03	2.56	1.3
	Multiple malformations	Invariant	1.41	0.07	1.33	5.1
	Genital system	Invariant	1.77	0.00	1.76	0.2
	Limb	Invariant	3.42	0.03	3.39	0.9
Additional conditions	Congenital hypothyroidism	Country rate	0.21	0.00	0.21	0.0
	PDA assoc w prematurity	Invariant	0.30	0.00	0.30	0.0
	Pyloric stenosis	Country rate	0.87	0.00	0.87	0.0
Single gene disorders	Dominant	Invariant	1.40	0.00	1.40	0.0
	X-linked	Invariant	0.05	0.00	0.05	0.0
	Recessive (baseline)	Invariant	1.95	0.29	1.66	14.9
	Consangunity-related	Country rate	6.50	0.97	5.53	14.9
	Sickle cell disorders	Country rate	2.75	0.00	2.75	0.0
	Thalassaemias	Country rate	0.42	0.00	0.42	0.2
Genetic risk factors	Rhesus haemolytic disease	Country rate	1.20	0.30	0.90	25.0
	G6PDd kernicterus	Country rate	1.30	0.00	1.30	0.0
Estimated global total			39.8	3.1	36.6	7.9

Available interventions

There are only three possible outcomes for early-onset congenital disorders in the absence of intervention - fetal death, premature death, and life with some degree of disability.

Table 2.11 summarises the evolution of the interventions listed in Table 2.3 by disorder group and decade. The timeline indicates *introduction* of the methods: this does not equate to their universal deployment, even in high income settings.

With these interventions the number of possible outcomes increases to six:

1. Affected birth converted into unaffected birth, or avoided, by pre-conception intervention
2. Affected birth avoided by intervention during pregnancy
3. Stillbirth/fetal death (pregnancy loss after 20 weeks' gestation)
4. Early death (neonatal, infant, under-5 death)
5. Disability (classed here only as severe, mild/moderate, or well on treatment)
6. Effective cure (enabling near-normal length and quality of life, even with residual problems)

Improvements in diagnosis and care not only reduce the birth prevalence of affected infants; they also prolong the survival and ameliorate the levels of disability of children with incurable disorders, and so cause a steady increase in the cumulative number living with these disorders and requiring appropriate care. The evolution of this effect needs to be quantified in order to assess service needs.

Table 2.11. Evolution over time of the interventions available for congenital disorders

	Decade							
Intervention	**1940s**	**1950s**	**1960s**	**1970s**	**1980s**	**1990s**	**2000s**	**2010 -**
Pre- pregnancy interventions								
Rhesus disease		Exchange transfusion →		anti-D, Rh-ve mothers →				
For NTD (and other?)					Vitamin supplements	FA flour fortification →		
Single gene disorders				Counselling on recurrence risk →				
Tay-Sachs & Hb disorder				Pre-conceptn carrier screen →				
Antenatal risk identification & prenatal diagnosis								
Chromsomal disorders				Amnio, older mothers	Serum markers, 1st trimester PND	US markers, universal screen	1st trimester screen, pre-preg diagn →	
Neural tube defects				Amnio & AFP	Maternal serum AFP, ultrasound	Routine fetal anomaly scan	1st trimester US →	
Congen heart disease						4-chamber scan →		
Other congen malfns					Routine fetal anomaly scan →			
Hb disorders				Carrier screen, 2nd trim PND	CVS & DNA: 1st trim PND →		Pre-pregnancy genetic diagnosis	
Other single gene						CVS & DNA: 1st trimester PND	→	
Rhesus disease			Amnio, IU transfn →					
Diagnosis & care, live-born affected								
Chromosomal disorders		Antibiotics, basic care	Mandatory care →			Repair of CHD →		
NTD (spina bifida)			Selective closure	routine closure →				
Oro-facial clefts	Surgical repair →							
Pyloric stenosis	Surgical repair →							
Congen heart disease	Repair PDA →		Repair "mild" defs	Cardiac echo	Repair "complex" defects (open heart) →		Non-invasive repair →	
Limb	Orthopaedics →							
Other congen malfns			NN exam: surgical repair →			Improved techniques →		
Congen hypothyroidism			NN screen, Rx →					
Hb: thalassaemia		Antibiotics, basic care	Transfusion, parenteral Fe chelation →			Oral iron chelation →		
Hb : sickle cell			→		NN screen & care →			
Some metabolic disorders			NN screen, Rx →					

Survival and early mortality with optimal care and with none

Table 2.12 shows the main sources used in the Global Database for estimating survival in the absence of care, and with optimal care. The upper age limit of the observational data is also shown.

Table 2.12. Principal sources of data on survival with congenital disorders

Main group	Diagnostic group	Optimal survival	Recorded to age:	No-care survival
Chromosomal disorders	Down syndrome	Baird and Sadovnick (1987), (1988)	Life time	Penrose (1949); Carter (1958); Stevenson (1959)
		Frid, Drott *et al.* (2004).	1 yr	
	Other trisomies	Wu, Springett *et al.* (2013)	5 yr	Lethal
	Other autosomal	Est. 10% <Down		Est. 10% <Down syndrome
	Turner syndrome	Price, Clayton *et al.* (1986) Stochholm, Juul *et al.* (2006)	60 yr	Mortality est. 2 × optimal care
	Klinefelter syndrome	Bojesen, Juul *et al.* (2004)	Assumed normal	Bojesen, Juul *et al.* (2004)
Congenital malformations	Anencephaly	Lethal		Lethal
	Spina bifida & encephalocele	Hunt and Oakeshott (2003);	30 yr	Lorber (1971); Laurence and Tew (1971)
		Bowman, McLone *et al.* (2001) Tennant, Pearce *et al.* (2010)	20 yr	
	Oro-facial clefts	Christensen, Juel *et al.* (2004)	Life time	Smile Train data; Raju (2000)

Main group	Diagnostic group	Optimal survival	Recorded to age:	No-care survival
	Congenital heart disease	Wren and O'Sullivan (2001) Tennant, Pearce *et al.* (2010); Wren, Irving *et al.* (2012)	20 yr	C Wren personal communication
	CNS not NTD	Tennant, Pearce *et al.* (2010); Skjaerven, Wilcox *et al.* (1999); Lie, Wilcox *et al.* (2001)	20 yr: Tennant, Pearce *et al.* (2010) Life-time: Skjaerven, Wilcox *et al.* (1999) and Lie, Wilcox *et al.* (2001)	Expert opinion (AC & BM)
	Eye			
	Ear, face, neck			
	Respiratory system			
	Digestive system			
	Abdominal wall defects			
	Urinary system			
	Multiple malformations			
	Genital system			
	Limb			
Additional conditions	Congenital hypothyroidism		Assumed normal	Classical literature
	PDA assoc w prem			Campbell (1968)
	Pyloric stenosis			Lethal
Rare single gene	Dominant	Costa, Scriver *et al.* (1985)	Life time estimates	Estimates based on Baird, Anderson *et al.* (1988)
	X-linked			
	Rare recessives			
Consanguinity-associated.		Bundey and Alam (1993)	5 yr	Bittles and Neel (1994)
Haemoglobin disorders	Hb thalassaemia	Modell, Khan *et al.* (2000) and (2008)	45 yr	Modell and Berdoukas (1984)
	Hb sickle cell	Platt, Brambilla *et al.* (1994)	life time	Fleming, Storey *et al.* (1979)
Genetic risk factors	Rhesus negativity	Bhutani, Zipursky *et al.* (2013)	Assumed normal	Stevenson (1959)
	G6PD deficiency	WHO (1985b)		WHO (1985b)

Survival is usually expressed as percentage of affected individuals born in a given year who are still alive by given age intervals, and charted as a survival curve. Age intervals used for congenital disorders are usually birth to 1 month, to 1 year, to 5 years and then by 5-year intervals. Mortality is the complement of survival. As an example, Figure 2.3 shows the survival curves used for oro-facial clefts with optimal care and no care.

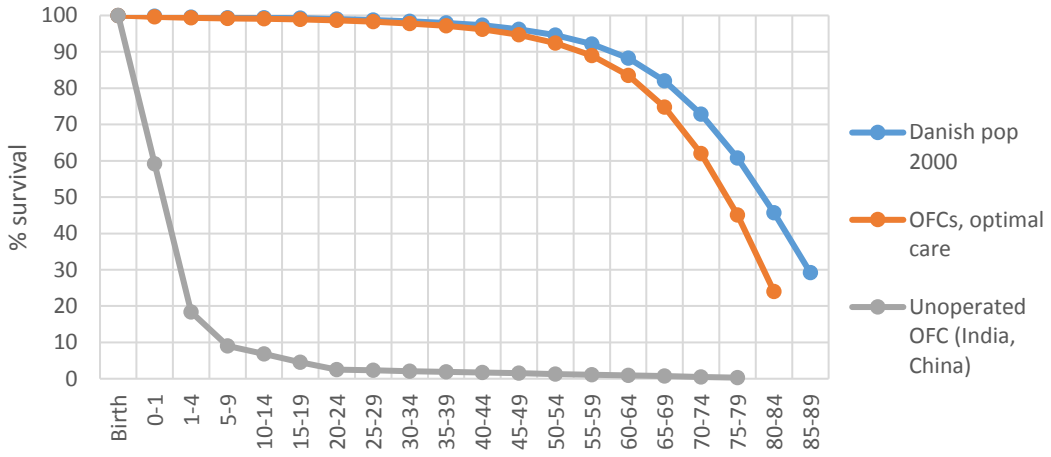

Figure 2.3. Survival with oro-facial clefts (OFCs) with no care (China, India) and optimal care (Denmark). (Calculations of P Mossey and B Modell, based on analysis of accounting data from the Smile Train NGO[38], and Christensen, Juel *et al.* (2004)[39]). Mean life expectancies calculated from the curves are: OFC with no care, 4.4 years. OFC with optimal care 74.5 years, compared with average 79.5 years for the Danish population. Importantly, the curve also shows that residual problems can continue to affect people with corrected congenital malformations. For this reason cure is described as "effective cure" in the Global Database.

[38] www.smiletrain.org.uk

[39] Christensen found that people born with oro-facial clefts had a life time 1.4 relative risk of dying, with only minor differences related to sex, age or year of birth. This relative risk was applied to WPP survival data for the Danish Population in 2000 (when the observations were made) to construct the survival curve.

The ideal survival curve would cover the entire potential life span from birth, but Table 2.12 shows that this data is not always available. However, for most congenital disorders mortality is highest within the first five years of life, the period for which survival data both with no care and with optimal care is most complete and most reliable. Therefore current data allows reasonably reliable estimation of early mortality in the Global Database. However it must be kept in mind that available survival data usually lags behind the current situation, especially when there are significant technical advances in care.

Calculating early mortality – neonatal, infant and under-5

Table 2.13 shows rates based on the literature for neonatal, infant and under-5 mortality with optimal care, and in the absence of care. Details of the way these estimates are obtained are given in the articles on different disorder groups. The rates in Table 2.13 are used in the Global Database to calculate annual neonatal, infant and under-5 deaths from annual affected births. However, most reports, including those of untreated disorders in the older literature, originate from high income settings where basic supportive care was available. Mortality estimates based on the rates in Table 2.13 are therefore likely to under-estimate mortality in lower-income settings. No allowance is made for this in the calculations.

Total versus attributable deaths

To avoid double-counting it is important to allow for the overlaps inherent in multiple causes of death[40]. For assessing *total deaths* of people with a given disorder, all deaths of affected individuals must be included, whatever the cause. However when the aim is to assess *attributable deaths* - deaths that are *specifically due to* a disorder – background mortality should also be considered, because some affected individuals who would have died of their disorder in fact die earlier from unrelated causes, and the proportion of such deaths varies with place and time. That is, mortality should be divided into deaths attributable to the disorder and deaths from other causes. No similar adjustment is needed for survival.

Since the current aim is to estimate attributable deaths, background mortality in the relevant country at the time the data was collected (from WPP) is has already been allowed for in Table 2.13, which therefore represent mortality due to the disorder in the absence of any other cause to obtain disorder-specific attributable mortality[41]. In the Global Database, the resulting “baseline” mortality rates are adjusted for local background mortality, to obtain country-specific estimates of attributable mortality (See *Annex A4: Calculation of attributable early mortality* for a worked example).

To obtain attributable early deaths, numbers are adjusted for deaths from other causes using country rates for neonatal, infant and under-5 deaths. The adjustment makes relatively little difference in countries where early background mortality is low, but when background mortality is high a sizeable difference is observed. Figure 2.4 shows estimated under-5 mortality in 2010-14 calculated in this way, to illustrate differences between regions and disorder groups.

[40] When a single cause is given this should be the *underlying cause of death* defined as “the disease or injury which initiated the train of morbid events leading directly to death” (www.who.int).
[41] Since most survival data, including that for the no-care situation, was collected in high income settings with low early mortality, this adjustment makes relatively little difference for most disorder groups.

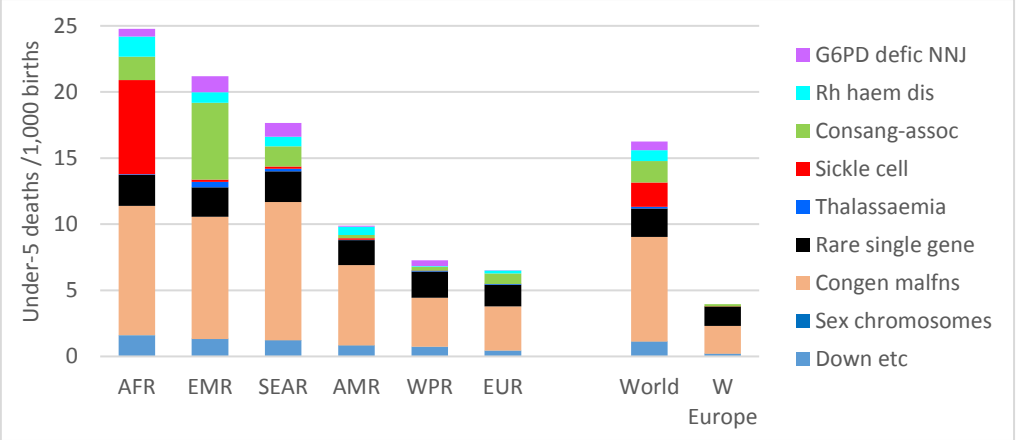

Figure 2.4. Estimated under-5 deaths due to congenital disorders, 2010-15, by main disorder group. World by WHO region, in descending order of total attributable under-5 mortality

Table 2.13. Estimates of early mortality and mean life expectancy by disorder group, with no care and with optimal care

Main group	Disorder group	No care: % mortality at:			Optimal care: % mortality at:		
		1 mo	1 yr	5 yrs	1 mo	1 yr	5 yrs
Chromosomal disorders	Down syndrome	35	45	69	1	2	6
	Other trisomies	92	100	100	64	92	100
	Other autosomal	42	51	72	11	12	15
	Turner syndr	0	0	0	0	0	0
	Klinefelter syndr	0	0	0	0	0	0
Congenital malformations	Anencephaly	100	100	100	100	100	100
	Spina bif & e'cele	80	90	93	17	25	33
	Oro-facial clefts	32	41	82	1	1	1
	Very severe CHD		96	97		63	70
	Severe CHD		64	65		9	10
	CNS not NTD	95	95	95	21	27	31
	Eye	28	33	36	0	1	3
	Ear, face, neck	2	7	8	6	6	6
	Respiratory	30	35	40	37	42	42
	Digestive system	65	70	75	14	16	17
	Abd. wall defects	95	100	100	16	19	19
	Urinary system	10	25	40	11	12	12
	Multiple malfns	54	59	61	40	50	53
	Genital system	0	0	0	0	0	0
	Limb	1	2	7	3	3	3
Additional conditions	Congenital hypothyroidism	0	25	55	0	0	0
	Prem-assoc PDA	15	30	32	0	0	0
	Pyloric stenosis	0	100	100	0	0	0
Rare single gene	Dominant		60	100		34	50
	X-linked		35	40		20	25
	Rare recessives		40	50		30	35
Consanguinity	Consanguinity-associated		40	50		30	35
Haemoglobin disorders	Sickle cell disease		20	80		4	5
	Beta thalassaemia		30	90		1	1
Genetic risk factors	Rhesus haem dis.		75	80		0	0
	G6PDd kernicterus		75	80		0	0

Note. Figures for mean life expectancy with optimal care are for the situation in the absence of preventive interventions (e.g. prenatal diagnosis). Since prenatal diagnosis leads to termination of pregnancy of the most severely affected fetuses, it tends to increase the observed survival of life-born affected infants.

Disability and cure with optimal care, and with none

Definitive cure of conditions currently included in the Global Database is limited to correctable congenital malformations and neonatal jaundice. Survivors with most other

disorders live some disability. This can range from well on care[42] (e.g. congenital hypothyroidism with regular replacement treatment) to the very severe (e.g. associated severe physical and mental disability). Because of this diversity, in the Global Database quantification of physical disability is limited to estimates of the proportion of survivors at age five with severe disability (including shortened life expectancy), mild to moderate disability (with less or no effect on life expectancy), well on treatment (a near-normal life expectancy with no physical or mental disability)[43] and effectively cured.

Table 2.14 shows the estimated proportion of each outcome by disorder group as used in the current database. However it is hard to obtain the desired rates from the literature (oro-facial clefts are an exception) and they need much improvement. In the current Global Database they are used mainly as place-holders.

Table 2.14. Provisional estimates of disability with optimal care and no care used in the Global Database

Disorder group	Optimal care				No care	
	Effective cure	Well on treatment	Residual mild-moderate disability	Residual severe disability	Moderate disability	Severe disability
Down syndrome				100		100
Other autosomal				100		100
Turner syndrome			100		100	
Kleinfelter syndrome			100		100	
Spina bifida and e'cele	0		0	100	0	100
Oro-facial clefts	80		20	0	0	100
Congenital heart disease	80		12	8	80	20
CNS not NTD	0		30	70	0	100
Eye	50		50	0	0	100
Ear, face, neck	60		40	0	0	100
Respiratory	90		10	0	0	100
Digestive	90		10	0	0	100
Abdominal wall	95		5	0	0	100
Urinary	95		5	0	50	50
Multiple malformations	5		25	70	0	100
Genital	95		5	0	100	0
Limb	95		5	0	90	10
Congenital hypothyroidism	0	100	0	0	0	100
PDA assoc w prematurity	100		0	0	80	20
Pyloric stenosis	100		0	0	lethal	lethal
Dominant			20	80	20	80
X-linked			25	75	25	75
Recessive (not consanguinity-associated		2	10	88	10	90
Consanguinity-associated		2	10	88	10	90
Sickle cell disorders			50	50	10	90
Thalassaemias		30	60	10	10	90
Rhesus haemolytic disease	100				50	50
G6PDd kernicterus	100				50	50

Outputs of the Method

The Global Database generates the following outputs, designed to meet the needs of policy-makers. As with inputs, they are divided into outputs at age 5 and long-term outputs.

Outputs to age 5:

- Baseline affected birth prevalence (scale of the problem)
- Potential outcomes in the absence of intervention (the no-care situation)

[42] Normal life expectancy and quality of life as long as treatment is maintained.
[43] Not included in the 2015 version of the Global Database: to be included in the 2016 version.

- Effects of interventions before birth
- Actual birth prevalence and birth outcomes
- Effects of interventions after birth on survival and disability
- Actual outcomes for live born: early deaths, disability, cure

Long-term outputs:

- Estimated years of life lost, lived with disability or lived cured.
- Estimated number and age distribution of living affected individuals.
- Future projections: potential effects of present policies, and of changes in policy on numbers and outcomes.
- Improved assessment of costs and benefits

Expressing Outputs for Various Audiences

Though the primary target is those seeking to formulate policy in this area, they are not the only people with an interest, and different audiences prefer to use data in different ways. Tailoring the presentation of outputs requires several decisions to be made.

- Rates or numbers? Rates (usually /1,000 births) are best for comparisons between countries, regions and time periods. The primary emphasis in these methods articles is on rates, to enable comparisons between WHO regions and sub-regions. However, for planning purposes policy-makers usually also want numbers. Country-specific rates and numbers are both available in the online presentation.
- Rates may be calculated using different denominators. Population number is the usual denominator in a public health context (e.g. the incidence of a disorder = new cases /100,000 population/year). By contrast, annual births are the usual denominator for rates for congenital disorders (e.g. affected births or under-5 deaths /1,000 births), and this convention is used throughout the Global Database. [44] Expression in terms of births /1,000 enables more reliable comparisons between countries and regions than rates /100,000 population (See *Annex A3: Different ways of expressing incidence*).
- When it is desirable to harmonise Global Database rates with major public health enterprises such as the Global Burden of Disease (GBD) study, they can be re-calculated as rates /100,000 population. Alternatively, as the GBD reports numbers as well as rates, GBD numbers can be related to WPP annual births to obtain rates /1,000 births. This method is used for the comparison between GBD and Global Database estimates of early mortality summarised in *Annex A1: Comparison of GBD and Global Database under-5 mortality estimates*.
- The use of births as a denominator is extended in the Global Database to the description of costs and benefits. For example years of life lost, lived with disability or lived cured are calculated in terms of average implications for each member of the relevant birth cohort.
- Tables or charts? Tabular data is required for planning purposes, and can be used to produce graphical visualisations, but can also lack communicative immediacy for the general reader. Charts can convey complex information at a glance and so are best for introducing an argument or summarising results. However in this context they can

[44] Affected birth prevalence is calculated in congenital anomaly registries as rate /10,000 total births (stillbirths and live births). For use in the Global Database these are translated to rates /1,000 total births. However the Global Database uses WPP birth estimates for calculating affected births, but these apply only for live births. This calculation therefore results in modest under-estimation of numbers affected.

only be used for comparing rates, because vast differences in population sizes mean that large populations dominate any chart showing absolute numbers. Therefore when relevant a supporting table is provided in the *Table Annexe*.

Outputs to 5 years of age

This section gives examples of each of the above outputs, charted by WHO region. Rates for Western Europe are included as the global reference region for assessing effects of interventions. See the *Table Annexe* for supporting data. All rates shown are for 2005-09, calculated using WPP 2012 revision.[45]

Baseline birth prevalence and no-care birth outcomes

Figure 2.2 shows estimated baseline birth prevalence by WHO region and main disorder group. Despite inter-country differences baseline birth prevalence is relatively constant for any given country, and provides an objective measure of the scale of the problem. All outcomes, whether with no care or optimal care, must fit into the "envelope" it provides. The charts that follow demonstrate this central role of baseline birth prevalence.

Figure 2.5 shows the distribution of fetal death/stillbirth, under-5 death, and survival with disability by 5 years of age in the no-care situation, and Figure 2.6 shows estimated actual outcomes in 2010-14.

Though errors are likely in estimating outcomes, an error in one compartment simply shifts numbers into other compartments without altering the total envelope. For example, under-estimation of mortality increases estimated numbers living with disability (or cured) and vice versa.

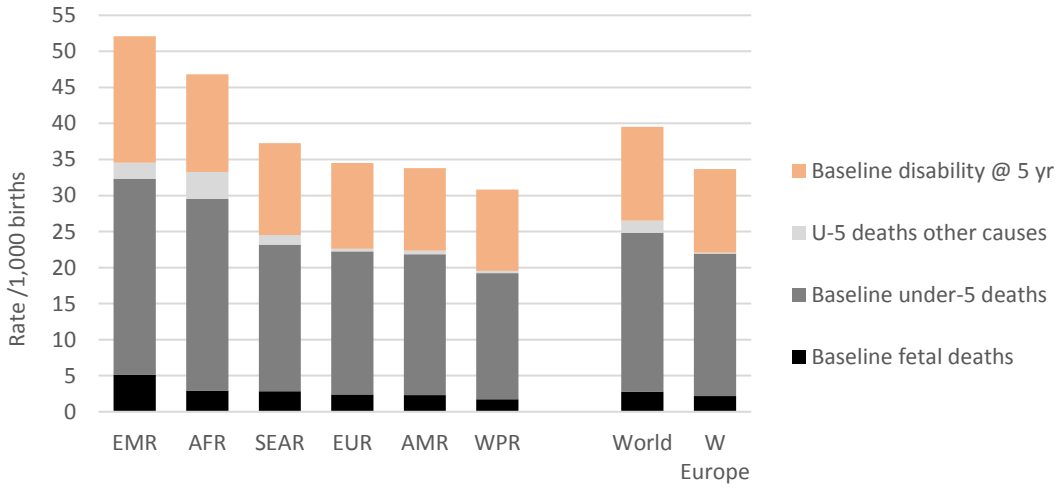

Figure 2.5. Total congenital disorders. Estimated outcomes at 5 years of age *in the absence of intervention* per 1,000 live births. World by WHO region, ranked in descending order of total baseline birth prevalence. The total height of the columns shows baseline (potential) birth prevalence. All outcomes fit within the envelope this provides.

[45] Update is planned using rates from revision of the Global Database

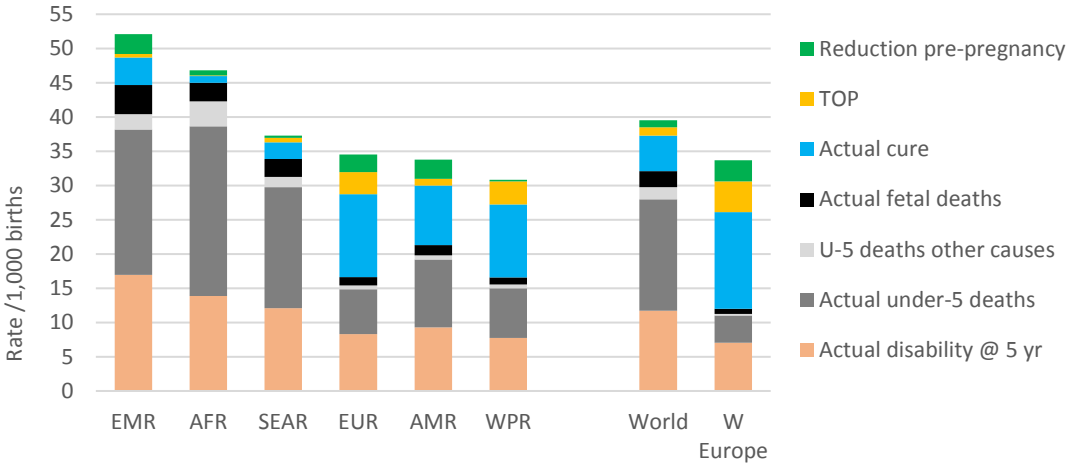

Figure 2.6. Total constitutional congenital disorders. Estimated actual outcomes. World by WHO region, ranked in descending order of total baseline birth prevalence. (TOP = termination of pregnancy for fetal impairment.)

Effect of interventions before birth

Figure 2.7 shows estimated reduction in total affected birth prevalence due to pre-birth intervention in 2010, by type of intervention. Globally, the largest contributions were from anti-D for rhesus negative mothers and termination of pregnancy for fetal impairment. The contribution of folic acid food fortification was relatively small because it only began to be implemented on a large scale around 2007. The effect of genetic risk detection and counselling is relatively small because in most cases risk is only detected retrospectively, i.e. after the diagnosis of an affected child.

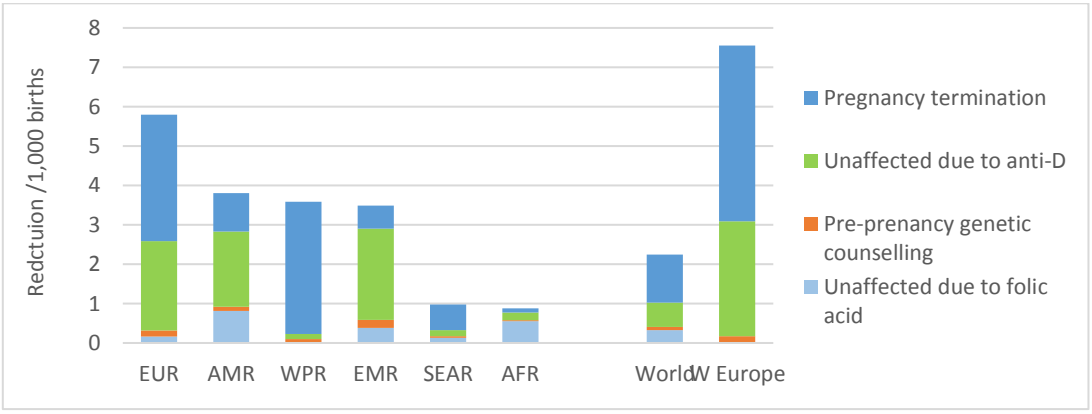

Figure 2.7. Estimated reduction in affected births /1,000 due to interventions before birth, 2010-14. WHO regions ranked in descending order of total reduction.

Actual birth outcomes: fetal death /stillbirth

This outcome is covered fully here because it is not addressed elsewhere in this series.

The strong association between congenital disorders and stillbirth (see Table 2.10) means that congenital disorders contribute disproportionately to stillbirths: globally in 2005-09 they represented 3.9% of total births (range 2.6% in Asia Pacific HI region to 5.8% in the Gulf States), but over 14% of stillbirths (range 10.5% in South East Asia to 52% in the Gulf States) (Table 2.15). The main potential contributors to fetal death are chromosomal disorders, neural tube defects, single gene disorders and rhesus haemolytic disease. Pre-birth interventions have most effect on these disorders and so are particularly effective in reducing stillbirth rates. Table 2.16 shows that globally in 2005-09 around 20% of potential

fetal death/stillbirths due to congenital disorders were avoided by interventions before birth (range 11.1% in AFR to 27.5% in Western Europe).

However the uncertain definition of stillbirths affects all estimates. For example the contribution of congenital disorders to stillbirth may be over-estimated in the Global Database because EUROCAT fetal death rates (defined as death in utero after 20 weeks' gestation) are used as a proxy for stillbirths, while rates from Cousens, Blencowe *et al.* (2011) – stillbirth defined as death in utero after 28 completed weeks' gestation – are used as denominator.

Table 2.15. Estimates of annual stillbirths and proportion associated with congenital anomalies and congenital disorders. Rates in 2005-09. Stillbirth rates from Stanton, Lawn *et al.* (2006) and Cousens, Blencowe *et al.* (2011). Annual births from WPP 2012 revision.

WHO region	Annual births 1,000s	Stillbirths %	Annual stillbirths	Congenital anomalies		Congenital disorders	
				% of total births	% of stillbirths	% of total births	% of stillbirths
Algeria, W Sahara	830	1.13	9,464	2.7	14.2	4.1	32.2
Sub-Saharan Africa	28,338	2.89	842,250	2.5	4.6	4.9	10.8
Southern Africa	1,720	1.99	34,851	2.4	5.6	3.5	12.1
AFR	30,888	2.79	886,565	2.5	4.8	4.8	11.1
North America	4,631	0.30	14,004	2.7	29.7	3.2	38.1
Caribbean	730	1.24	9,196	2.4	8.3	3.5	14.7
Central America	4,942	0.81	40,482	2.6	12	3.3	21.3
South America	4,476	1.05	47,539	2.8	13.5	3.6	23
S America HI	988	0.61	6,045	2.8	20.7	3.3	26.1
AMR	15,767	0.74	117,265	2.7	14.9	3.4	23.7
Gulf states	824	0.69	5,758	2.7	18.7	5.8	52.9
N Africa /Middle East	8,240	1.55	129,767	2.6	8.8	4.6	26.3
Afghanistan /Pakistan	5,712	4.11	244,770	2.8	4.6	6.1	15.3
Somalia, Djibouti, S Sudan	441	2.94	13,370	2.5	4.6	3.9	11.1
EMR	15,217	2.52	393,666	2.7	6.2	5.2	19.3
Western Europe	4,526	0.31	14,019	2.5	19	3.0	27.5
Central Europe	1,223	0.39	4,829	2.5	14.8	3.0	20.5
Eastern Europe	2,334	0.88	20,788	2.6	9.7	3.0	12.2
Turkey	1,297	1.16	15,178	2.3	7.6	3.6	20.7
Central Asia	1,671	0.88	14,831	2.6	15.1	4.0	36.7
EUR	11,051	0.63	69,646	2.5	12.6	3.2	22.9
South Asia	29,608	2.34	708,193	2.7	7.8	4.0	13.6
Southeast Asia	7,029	1.44	102,363	2.4	8.4	3.3	12
SEAR	36,637	2.16	810,556	2.6	7.9	3.8	13.4
East Asia	17,889	0.90	162,519	2.3	12.8	2.9	17.2
Southeast Asia	4,810	1.44	70,329	2.5	8.4	3.2	10.5
Asia Pacific HI	1,854	0.30	5,563	2.1	18.3	2.6	27.2
Oceania	260	1.45	3,824	2.5	9.5	3.4	16.4
Australasia	351	0.29	1,025	2.5	18	3.0	25.1
WPR	25,164	0.96	243,260	2.4	11.6	3.0	15.5
World	134,724	1.84	2,520,958	2.6	7.3	3.94	14.5

Table 2.16. Estimated no-care (potential) and actual fetal deaths due to constitutional congenital disorders /1,000 births, and per cent contribution to total stillbirths by WHO region

WHO region	Stillbirths /1,000 (WPP)	Baseline fetal deaths /1,000	Actual fetal deaths /1,000	Reduction /1,000	% reduction	Actual fetal deaths, % of total stillbirths
AFR	29.4	2.9	2.7	0.2	5	9.4
AMR	7.3	2.3	1.5	0.8	35	20.4
EMR	26.4	5.1	4.2	0.9	18	16.0
EUR	5.9	2.4	1.2	1.2	48	21.1
SEAR	22.3	2.8	2.6	0.2	7	11.9
WPR	8.2	1.7	1.0	0.7	42	12.4
World	19.1	**2.8**	**2.3**	0.5	16	12.3
W Europe	3.3	2.2	0.7	1.5	67	22.3

Figures 2.8 and 2.9 show no-care (potential) and estimated actual fetal deaths /1,000, by cause and WHO region. The largest reduction is in fetal deaths attributable to rhesus haemolytic disease.

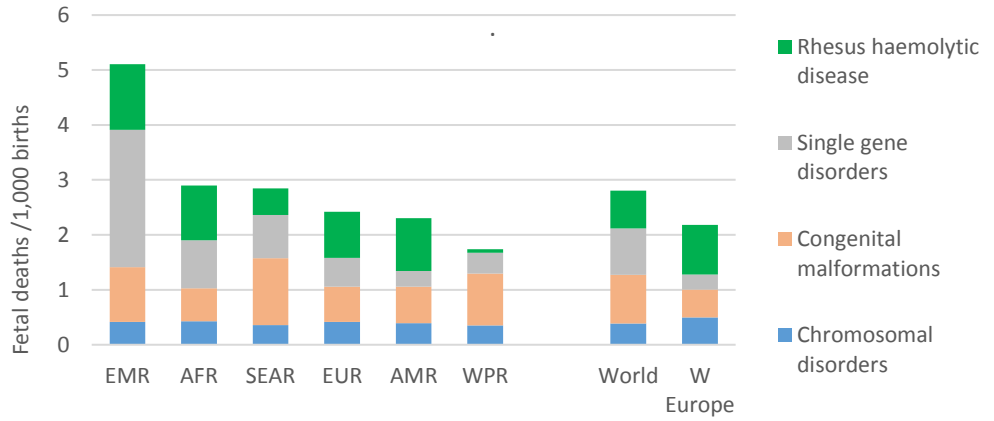

Figure 2.8. Estimated no-care (potential) fetal deaths due to constitutional congenital disorders /1,000 births. WHO regions ranked in descending order of total baseline rate.

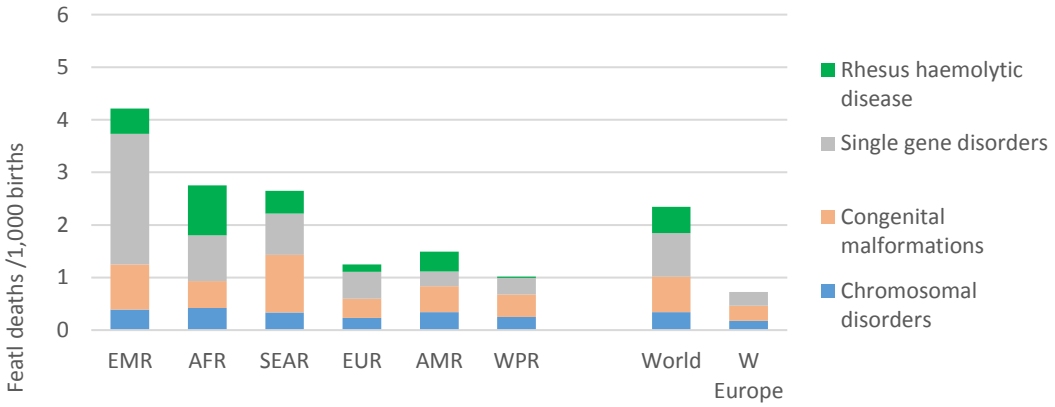

Figure 2.9. Estimated actual fetal deaths due to constitutional congenital disorders /1,000 births. WHO regions ranked by baseline rate.

Figure 2.10 shows reduction in fetal deaths /1,000 births by type of intervention. Interventions with most effect were anti-D for rhesus negative mothers, and termination of pregnancies likely to end in stillbirth. As with total affected births, genetic risk detection and counselling had a very limited effect.

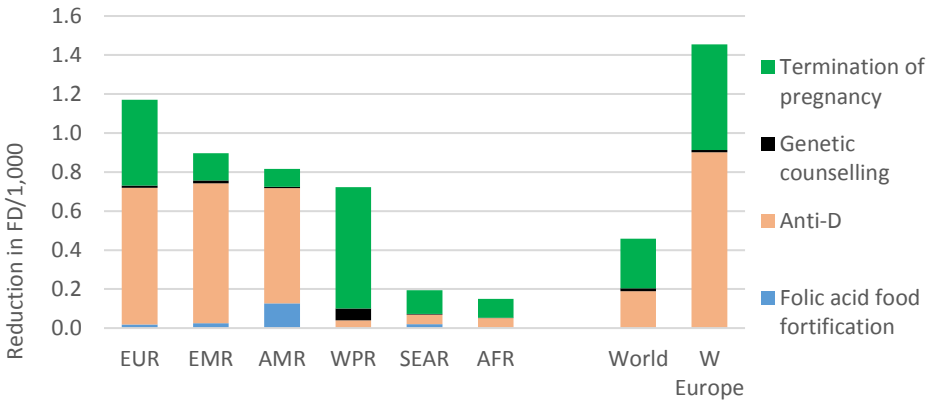

Figure 2.10. Estimated reduction in fetal death/stillbirths due to congenital disorders /1,000 births in 2010-14 by type of intervention. WHO regions in descending order of total estimated reduction.

Actual birth outcomes: affected live births

Figure 2.11 shows estimated actual live births /1,000 in 2005-09 by WHO region and disorder group. Total live births provide the envelope for assessing the effects of diagnosis and care.

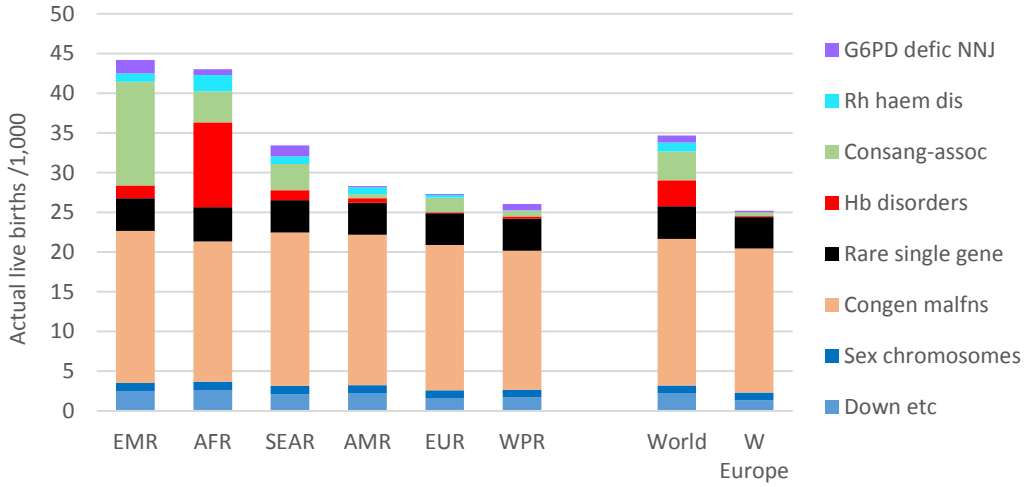

Figure 2.11. Estimated actual live births congenital disorders /1,000 by main group, 2010-14. WHO region in descending order of total affected birth prevalence. (Compare with Figure 2.2).

Early mortality

The discussion of early mortality is limited to under-5 mortality for the sake of brevity, and because it is the chosen indicator for progress towards the 4th Millennium Development Goal. Figures 2.12 and 2.13 show estimated potential and actual under-5 mortality due to congenital disorders by disorder group and WHO region.

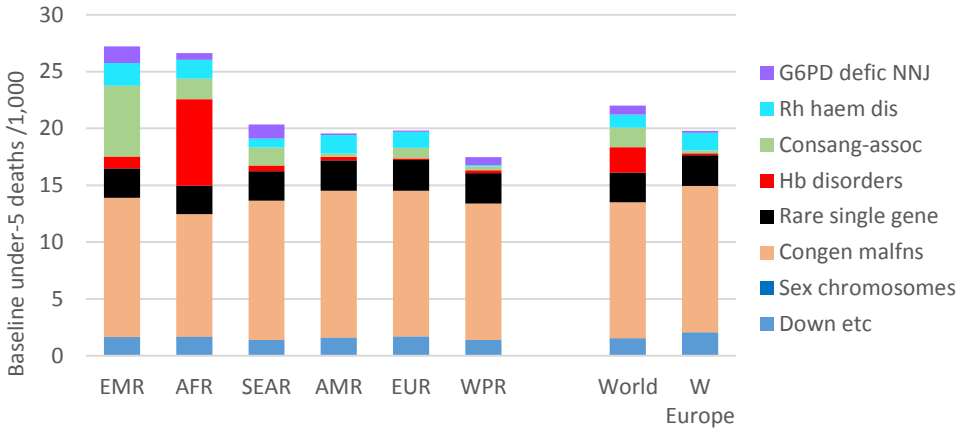

Figure 2.12. no-care (potential) under-5 deaths due to congenital disorders /1,000 births, by disorder type and WHO region.

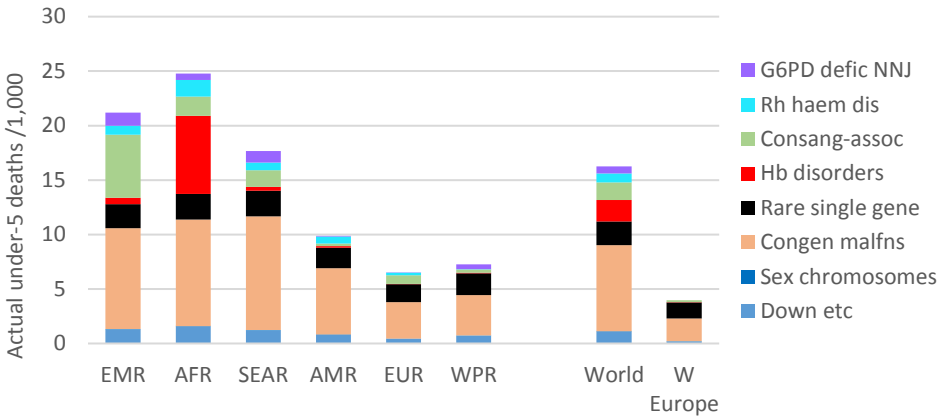

Figure 2.13. Estimated actual under-5 deaths due to congenital disorders /1,000 births 2010-14, by disorder type and WHO region.

Table 2.17 shows estimated per cent reduction in under-5 mortality by disorder group and WHO region in 2010-14. Estimates for Western Europe are included, as an indicator of the power of available interventions when fully deployed at the population level.

Table 2.17. Estimated % reduction in under-5 mortality due to congenital disorders by disorder group and WHO region, 2010-14.

	Congenital anomalies			Single gene disorders			2 risk factors		
WHO region	Down etc.	Sex chromo-somes	Congen malfns	Rare single gene	Hb disorders	Consang-assoc-iated	Rh haem dis.	G6PD defic. NNJ	Total constitutional
EMR	20	7	25	15	42	7	59	19	22
AFR	5	2	9	6	6	2	7	5	7
SEAR	12	4	15	10	27	4	10	14	13
AMR	47	15	53	29	52	16	61	54	49
EUR	74	24	74	38	72	15	84	75	67
WPR	48	17	69	26	75	16	62	38	58
World	27	9	34	17	12	6	29	19	26
W Europe	91	30	84	46	99	32	100	100	80

In Western Europe current interventions are estimated to have reduced baseline early mortality by around 80%. The reduction is greatest for chromosomal disorders, congenital malformations, haemoglobin disorders and the two genetic risk factors. The reduction in mortality due to other single gene disorders is far smaller. Consequently the total power of current interventions is lowest in populations with a high birth prevalence of single gene disorders.

Effective cure

Figure 2.14 shows estimated effective cure for around 5/1,000 children world-wide, and around 14/1,000 in high income settings. The most striking finding is that access to paediatric surgery can restore a normal life to around 14 otherwise severely affected children /1,000 births.

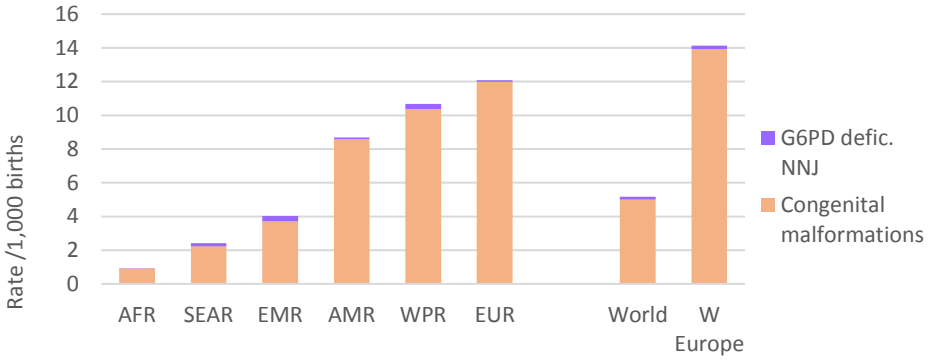

Figure 2.14. Estimated effective cure for congenital disorders /1,000 births, 2010-14, by cause and WHO region. Regions ranked in ascending order of cure /1,000 births. Cure for neonatal jaundice is due to early diagnosis and medical care. Cure for congenital malformations is almost entirely attributable to paediatric surgery.

Actual and perceived outcomes

Figure 2.6 summarises the distribution of actual outcomes in 2010, within the envelope of baseline birth prevalence, taking account of all interventions.

However the prevalence of congenital disorders tends to be perceived through their contribution to early death and disability. Termination of pregnancy, fetal and under-5 death and cure all remove cases and so reduce visibility. This leaves survival with disability as the primary perceived indicator of prevalence. Figure 2.15 shows that perceived burden may be reduced by as much as two-thirds when all available interventions are deployed. Reduced visibility may partly explain the low priority assigned to congenital disorders in most high income settings.

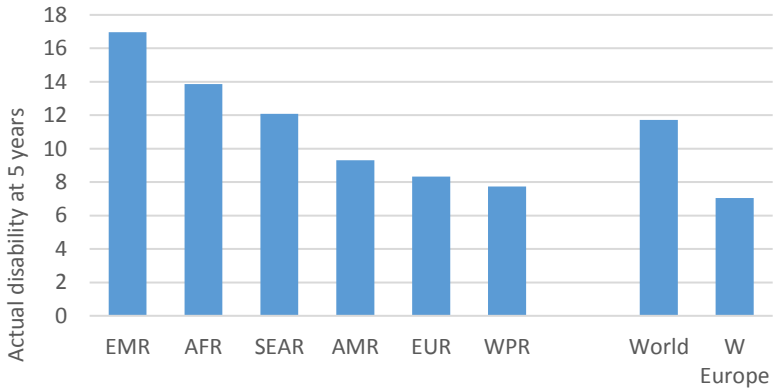

Figure 2.15. Estimated actual survivors with disability at 5 years /1,000 births, 2010-14, by WHO region, ranked in descending order of disability /1,000 births.

Table 2.18 shows the estimated total per cent reduction in adverse outcomes due to interventions at 5 years of age, in 2010-14. The greatest proportionate reduction is in under-5 deaths. There is far less reduction in disability.

Table 2.18. Per cent reduction in unfavourable outcomes below baseline rates due to interventions, by WHO region, 2010-14

WHO region	Fetal deaths	Under-5 deaths	Disability at 5 yr	Total adverse outcomes
EUR	48	67	30	53
WPR	42	58	31	47
AMR	35	49	19	38
EMR	18	22	3	15
SEAR	7	13	5	10
AFR	5	7	-2	4
World	16	26	10	20
W Europe	67	80	39	65

Discussion

Completeness of coverage

Ideally the Global Database would include all congenital disorders, as defined by WHO. However the range that can be included is limited because the modelling method used starts from baseline birth prevalence, i.e. births /1,000 in the absence of any intervention. At present the Global Database is limited to severe early-onset constitutional congenital disorders, because their baseline birth prevalence is known or can be estimated for most countries.

In future it is hoped to include adult-onset single gene disorders (e.g. familial cancers, familial hypercholesterolaemia, neurodegenerative disorders), bicuspid aortic valve[46], and disorders due to genetic risk factors (e.g. haemochromatosis). Their inclusion would greatly increase the estimated burden of congenital disorders.

Environmental congenital disorders are not currently included. This is because maternal exposure to risk varies with place, time and level of development of health services, and insufficient country-specific surveillance data is available to define baseline birth prevalences, or to quantify the effects of interventions. Table 2.19 shows the results of an attempt to provide at least provisional estimates at the request of WHO EMRO. Sufficient global data were available to make approximate estimates for the commonest congenital infections (rubella, toxoplasmosis, cytomegalovirus, syphilis, AIDS), but not for effects of other infections, other harmful exposures or nutritional deficiencies. Therefore in Table 2.19 estimates for congenital infections are doubled to obtain a general indication of the likely contribution of environmental disorders in 2010-14. This results in a global average baseline birth prevalence of around 13/1,000 - 25% of total early-onset congenital disorders. (The estimate of 20/1,000 for the African region reflects high estimates for syphilis and AIDS.)

Table 2.19. Estimated contribution of environmental congenital disorders to baseline birth prevalence of total early-onset congenital disorders, 2010-14

WHO region	Baseline affected births /1,000 births				Environ-mental % of total
	Total constitutional	Congenital infection	Estimated total environmental	Est total congenital	
AFR	46.8	10.0	20.0	66.9	30
SEAR	37.3	8.7	17.4	54.6	32
AMR	33.8	5.9	11.8	45.6	26
EMR	52.1	4.4	8.8	60.9	14
WPR	30.8	2.9	5.7	36.6	16
EUR	34.5	2.8	5.7	40.2	14
World	39.5	6.7	13.4	52.9	25
W Europe	33.7	2.4	4.8	38.4	12

[46] Bicuspid aortic valve is a congenital cardiac defect, probably dominantly inherited, that affects 1-2% of most populations and is one of the main causes of adult-onset aortic valve disease and/or aortic aneurysm.

Coverage of early-onset constitutional congenital disorders

Coverage differs according to disorder group as indicated in Table 2.20.

Table 2.20. Estimates of coverage of disorder groups included in the Global Database

Main disorder group	Disorder sub-group	Estimate based on	Comment on reliability of estimates		
			Baseline birth prevalence	Outcomes: HI settings	Outcomes: no care
Chromosomal disorders	Maternal age related (Down & other trisomies)	WPP % of mothers 35 plus	Near complete & reliable	Well documented in literature	Documented in older literature
	Rare chromosomal disorders	Wellesley, Dolk *et al.* (2012), EUROCAT	Some uncertainty due to diversity	Estimated (10% more severe than Down)	No data
	Sex chromosome disorders	Literature	Some uncertainty due to late diagnosis	Well documented in literature	Expert opinion based on HI literature
Congenital malformations	Neural tube defects	Country-specific rates from systematic reviews	Rates before vitamin supplementation: Generally reliable	Well documented in literature	NTD, older literature
	Oro-facial clefts				OFC, Smile Train data
	Other malfns included in EUROCAT	EUROCAT averages	Some under-estimation	Czeizel etc 1982, Tennant et al. 2010	Expert opinion
	3 additional groups	Older literature	Estimates only	Well documented	Expert opinion
Single gene disorders	Rare single gene disorders	Based on classical literature	Some under-estimation	Limited collective data in literature	Expert opinion & consanguinity effect
	Haemoglobin disorders	Modell and Darlison (2008)	Near complete	Well documented in literature	Well documented in literature
	Oculo-cutaneous albinism	Literature	Estimates for AFR only	Documented in South Africa	Documented in literature
	Consanguinity-associated	Prevalence of parental consanguinity (variable quality)	Quality of country estimates varies	Well documented (Bundey and Alam 1993)	Well documented (work of Bittles and others)
Disorders due to genetic risk factors	Rhesus haemolytic disease	Country-specific data on prevalence of Rh negativity	Reliability limited by uncertainty on risk of maternal immunisation	Well documented in literature	Documented in older literature
	Haemoglobin H disease	Global data on alpha thalassaemia carrier prevalences	Under-estimate (uncertain data)	Expert opinion	Literature from Thailand
	G6PD deficiency neonatal jaundice	Global data on carrier prevalences	Uncertain because of environment effects	Assumed normal	In older literature

The table shows that most estimates of baseline birth prevalence are acceptably reliable, but may be under-estimates for some disorder groups.

Most estimates of outcomes are evidence-based, but may be less reliable than baseline birth prevalences due to the limitations of available observational data.

Estimates for survival in a no-care situation are based on historical reports from high income countries, supplemented by expert opinion. A full table of estimates is included in *Annex F3: Estimating survival with congenital malformations in the absence of diagnosis and care*.

Probability of over- or under-estimation

Great care has been taken to exclude over-estimation (for example, see the method used to avoid double counting in *Article 7: Congenital malformations: birth prevalence and birth outcomes*), but there is a high probability of under-estimation.

1. Affected birth prevalence is calculated in congenital anomaly registries on the basis of total births (still births and live births). These are related to WPP live birth rates to obtain estimated affected birth prevalence: this leads to modest under-estimation.
2. The EUROCAT average rates used to calculate birth prevalences and outcomes are low estimates because there is demonstrable under-ascertainment in some participating registries.
3. Adjustment for uneven country contributions leads to an 8% increase in average EUROCAT rates. However no attempt has been made to adjust for this limitation, in order to remain as close as possible to the source data.
4. There is internal evidence in of selective under-ascertainment of terminations of pregnancy and fetal deaths in some countries.
5. Congenital disorders increase susceptibility to infection and other causes of early death. Since the ultimate cause of death is defined as the underlying cause, this manoeuvre probably leads to under-estimation of deaths due to congenital disorders.
6. Nevertheless, estimated early deaths are adjusted to “attributable” early deaths by subtracting deaths from other causes, calculated using local early mortality rates.

Possible future change in inputs

Table 2.21 shows that inputs least likely to change are birth prevalences of chromosomal disorders and congenital malformations. Inputs most likely to change are:

- Most recent (past 10 years) WPP demographic estimates
- Most recent EUROCAT (5 years) rates for fetal death and termination of pregnancy
- Birth prevalence of rare single gene disorders

Table 2.21. Likelihood of future change in inputs

Input	Likelihood of change
For every country	
WPP demographic data	There may be significant differences between WPP estimates and country observational data. There may be quite marked changes in estimates for the most recent 10 years.
Estimated access to services	Can be updated if any change in IMR, e.g. using country observations.
For every disorder group	
Baseline birth prevalence	Relatively constant
Intervention before pregnancy	Increase in genetic risk identification Policy change re anti-D, & folic acid food fortification
Termination of pregnancy	Policy change re TOP for fetal impairment
Fetal deaths	Rate falls with TOP for fetal impairment
Survival, if no care	Relatively constant
Survival, optimal care	Steady improvement for many conditions: evidence-based estimates may fall behind reality.
Adults: % living independently	More data is needed.
adults: reproductive success	Increases as total fertility rate falls, because it is expressed as a % of the population norm.

We conclude that as long as they are viewed as ball-park estimates intended to provide a broad general picture, the current estimates have reasonable long-term validity.

The importance of baseline birth prevalences

Specific features that justify a special epidemiological approach to constitutional congenital disorders are (a) the relative stability of their baseline birth prevalence in any given population, and (b) the fact that in the absence of intervention they cause early death or life-

long disability (i.e. there is no remission). Thus their baseline birth prevalence provides a solid foundation for estimating the effects of interventions that is not available for most other groups of medical conditions.

The relative stability of baseline birth prevalence also provides opportunities for some ways of expressing rates and outcomes that are uniquely applicable for congenital disorders. For example:

- Incidence is expressed as birth prevalence – affected births /1,000 total or live births – rather than in terms of new cases /100,000 population (as used e.g. by the Global Burden of Disease study).
- The fact that all outcomes must fit within the "envelope" provided by baseline birth prevalence is very helpful in evaluating rates for e.g. mortality, disability and cure.
- Burden can be expressed in years (or months) of life affected by congenital disorders per person in the relevant birth cohort (by contrast with e.g. number (or proportion) of years of life lost or lived with disability in the population).

Expressing burden in terms of years /person in the birth cohort

This is the preferred method used for describing burden in the Global Database because (a) annual births provides a more stable denominator than e.g. population number and (b) expressing outcomes in terms of months or years affected per person born facilitates intuitive grasp the burden of a disorder.

Figure 2.16 illustrates these points by comparing different ways of expressing the estimated impact of congenital *anomalies*. It is shown above that their baseline birth prevalence does not differ greatly between populations.

- The green columns in the chart show average years affected by congenital anomalies per person born. The differences between WHO regions are largely due to differences in local life expectancy.
- The brown columns show average years affected per 1,000 population (a form of expression commonly used in public health epidemiology). Because baseline birth prevalence is relatively constant, years affected /1,000 population are highest when life expectancy is short and fall as life expectancy increases. This somewhat counter-intuitive effect can complicate comparisons between populations and over time, and the estimated effect of interventions.

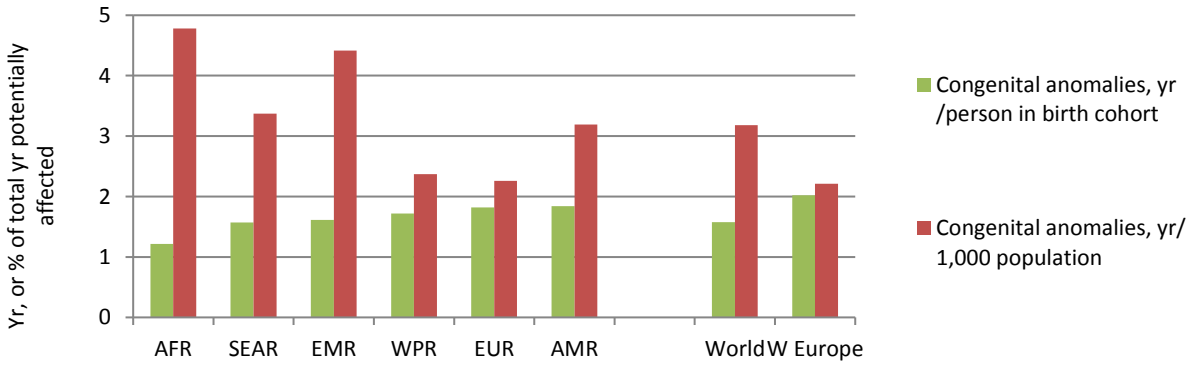

Figure 2.16. Different ways of expressing the potential life-time impact of total congenital *anomalies*. The estimates of years affected per person in the birth cohort are more truly comparable than years affected per 1,000 population

Bundling of outputs for different purposes

The way that outputs are bundled for presentation is determined by the object of the exercise. Outputs from the Global Database can be presented differently to suit different objectives.

The current purpose is to estimate numbers of individuals born annually with congenital disorders, and outcomes for these individuals, in the context of the administrative structure of the WHO. Therefore outputs are bundled by WHO region and notional sub-region. However if required they can also be bundled by e.g. GBD region. In addition congenital malformations are presented in terms of individuals with malformations (isolated or multiple) rather than numbers of congenital malformations. However if required (e.g. to calculate the need for clinical interventions) the Database can also generate numbers of congenital malformations

Comparison of under-5 mortality estimates with GBD

This topic is covered in *Article 1: Introduction: scope and general overview*.

Article 3: Methods for generating long-term estimates

Abstract

Decision-makers ideally need (1) an estimate of current patient numbers and age distribution; (2) projections of the effects of any policy change on patient numbers, and (3) an assessment of costs and benefits of different policy decisions. This article describes the additional inputs and methods required to generate such long-term estimates for constitutional congenital disorders, and gives some examples of outputs. All calculations start from estimated affected live births.

The following additional inputs are required:

- data on population number and age distribution from UN World Population Prospects (WPP);
- life-time survival curves obtained when necessary by extending existing survival data;
- mean life expectancy with no care and with optimal care, calculated from the life-time survival curves.

The above estimates are *prospective*. They predict future survival, and so long-term age distribution, of the cohort of patients born in a particular year. To calculate current patient number and age distribution, it is necessary to create *retrospective* survival curves that take account of the services available at the time each age group was born. The article includes the method used for generating these curves.

With these additional inputs, the estimates in *Article 2: Core methods for estimates to five years of age* can be extended to generate the following outputs: (1) estimated number and age distribution of living patients (treated and untreated); (2) calculation of average years of life affected by congenital disorders, and years lost, lived with disability or cured; (3) future projections of effect of policy change on these outputs.

Years of life lost, lived cured, or with disability due to congenital disorders are described in terms of average years affected per person in the relevant birth cohort, i.e. per person born in any given year. The application of this method indicates that: (a) current interventions reduce average loss of life due to constitutional congenital disorders per person born by 7.5% in AFR, 28% globally and 75% in Western Europe; (b) interventions that reduce mortality may increase numbers living with disability; (c) in high income settings such as Western Europe treatment (mainly paediatric surgery) adds at least 1.29 years of healthy life per person born.

We emphasise the need for improved quantitative methods for assessing disability, and the human costs and benefits of services for prevention and care of congenital disorders.

Introduction

Among the most important pieces of information sought by decision-makers seeking to plan services and policies for the future are:

- an estimate of current patient numbers and age distribution
- projections of the effects of any policy change on patient numbers
- an assessment of costs and benefits of different policy decisions.

The Global Database is capable of generating most of these estimates. The calculation starts from estimated live birth prevalence and available survival data (described in *Article 2: Core methods for estimates to five years of age*). It requires the following additional inputs:

- population number and age distribution

- life-time survival curves for each disorder group
- retrospective survival curves, taking account of the evolution of care over the past 70 years or so.

This article gives details of these additional inputs, and some examples of outputs.

Population number and age distribution

This data is required for calculating potential and actual patient numbers and age distribution. Estimates are available from WPP by 5-year intervals from 1950 to 2100 (see *Article 4: Uses of demographic and geographic data*). As an example, Figure 3.1 shows the change in population age distribution in Europe between 1950 and 2015.

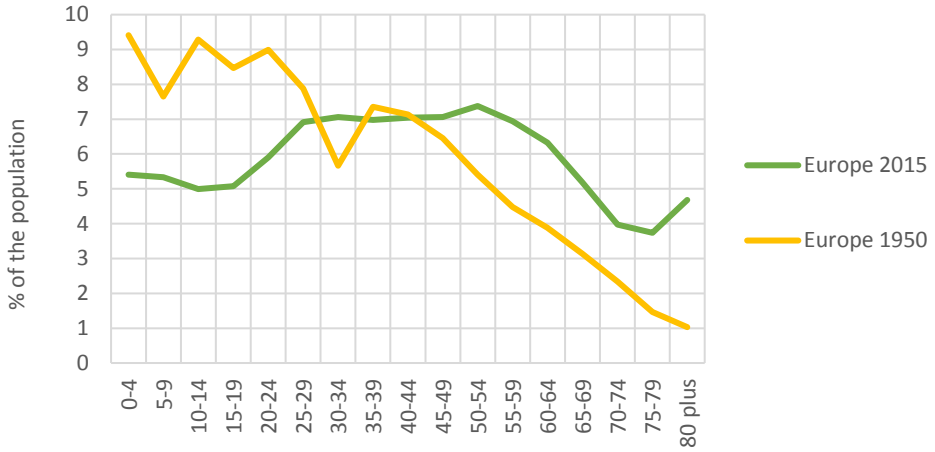

Figure 3.1. Population age distribution in Europe, 1950 and 2015. WPP estimates. Europe refers to the geographical region, not WHO EUR. Age distribution in 1950 is heavily weighted towards younger age groups. The striking deficiency in the 30-34 age group is due to the Second World War.

Figures 3.2 and 3.3 show estimated age distribution in 1950, and projected to 2050, for the world and Western Europe. Figures 3.4 and 3.5 show the corresponding change in proportion of the population under 12 and over 50 years of age. The comparison illustrates the changing pattern of need for medical services: the proportion under 12 years of age is the indicator of need for paediatric services: the proportion over 50 is the indicator of need for services for later-onset disorders of adult life (mainly non-communicable diseases).

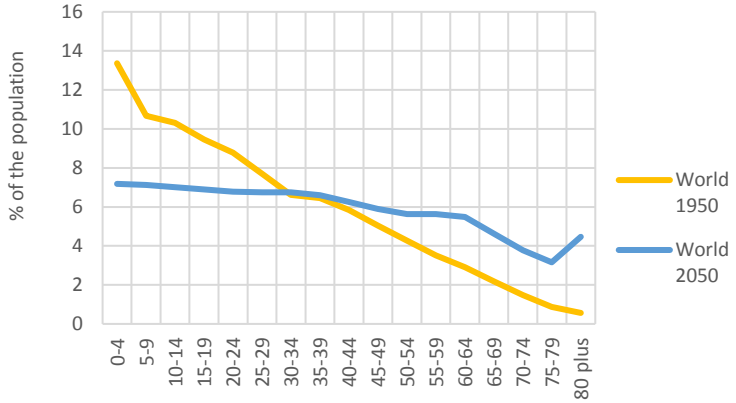

Figure 3.2. Age distribution of the world population in 1950, and projected for 2050. The 1950 distribution is typical for most populations in the past. Numbers were heavily weighted towards younger age groups, and total over 80 less than those aged 75-79. The projected distribution for 2050 shows typical future age distribution, with similar numbers in most age groups and an increasing proportion aged 80 plus.

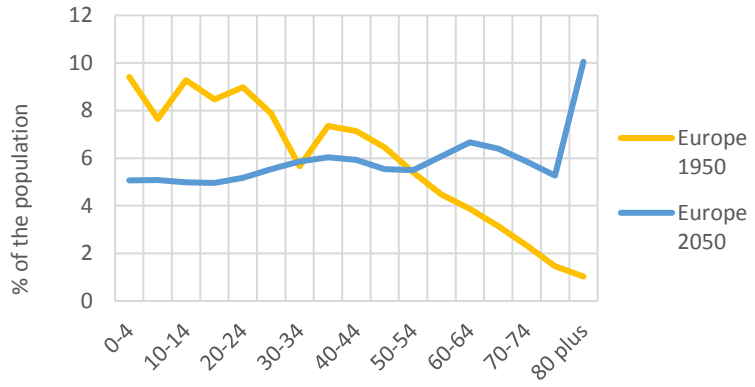

Figure 3.3. Age distribution of the population of Europe in 1950, and projected for 2050, illustrates the likely future increase in proportion of the population in the oldest age groups.

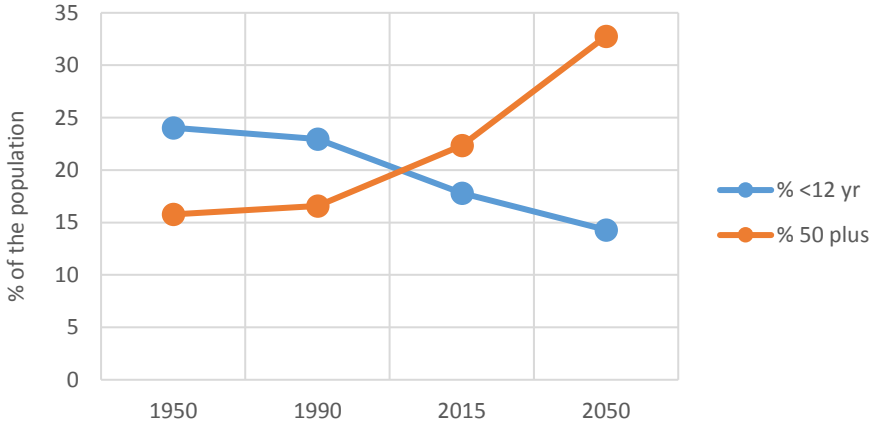

Figure 3.4. Proportion of the world population under 12 and aged 50 years or more, 1950-2050 (WPP estimates)

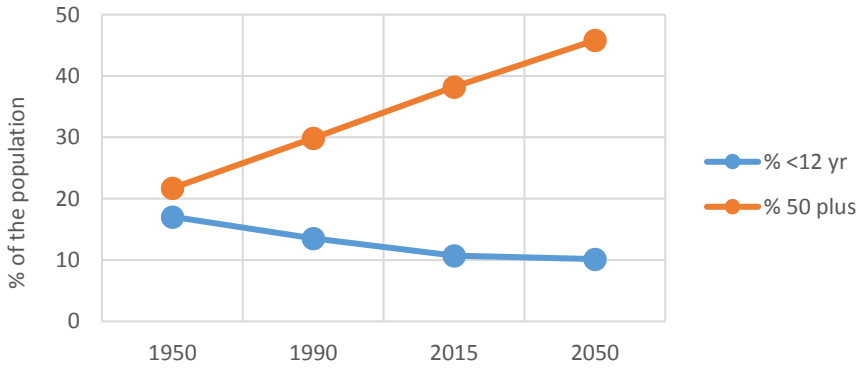

Figure 3.5. Proportion of the world population under 12 and aged 50 years or more, 1950-2050 (WPP estimates)

Obtaining life-time survival curves

Sources for survival estimates used in the Global Database are given in Table 2.12 of *Article 2: Core methods for estimates to five years of age*.

Life-time survival curves with optimal care are available for Down syndrome, spina bifida, oro-facial clefts and sickle cell disorders.[47] For most other disorders observational data are

[47] Some of these curves may be out of date because they were collected over many years, and new interventions may have become available in the interim.

only available to age 20 or 30. Survival curves for these disorder groups are completed by extrapolating the observed rate of attrition in the last full 5-year interval, to 80 years of age.

All survival curves used in the Global Database are adjusted in two ways: (a) for background under-5 mortality at the time and place the data were collected, to produce curves that represent mortality in the absence of any other cause of death[48], and (b) for the estimated effects of termination of pregnancy[49]. Since this option is not available in all countries, curves for global use must start from estimated survival in the absence of this service. The estimated effect of termination of pregnancy is added at a later stage in the calculation.

In high income settings normal survival is expected for curable congenital malformations, the additional conditions, and the two disorders due to genetic risk factors presently included.

The following figures show the resulting long-term survival curves for the main groups of congenital disorder, in the absence of care and with optimal care.

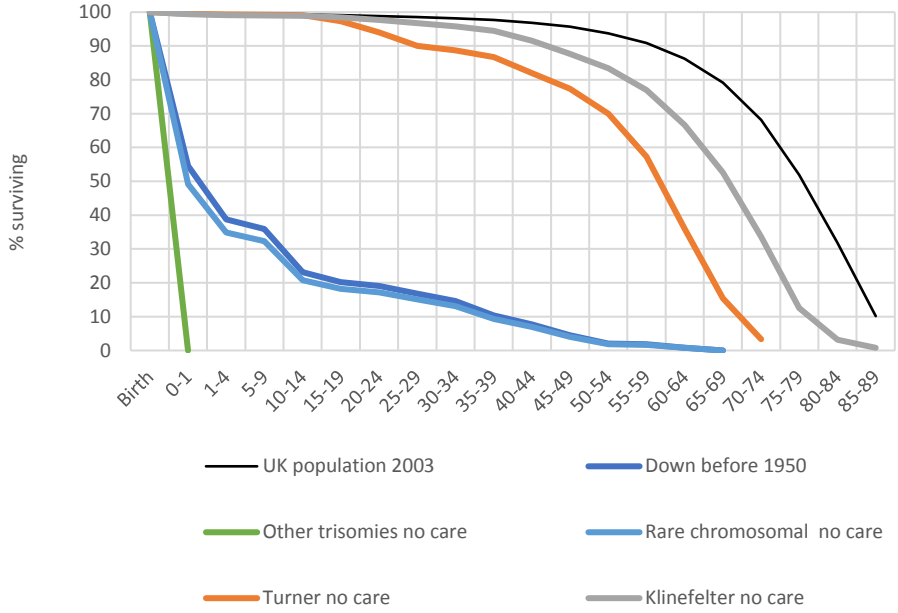

Figure 3.6. Chromosomal disorders. Estimated % survival with no care.

[48] Since most survival data, including that for the no-care situation, was collected in high income settings with low early mortality, this adjustment makes relatively little difference for most disorder groups.
[49] For details of this adjustment see *Article 8. Congenital malformations 2: estimating outcomes of live births*.

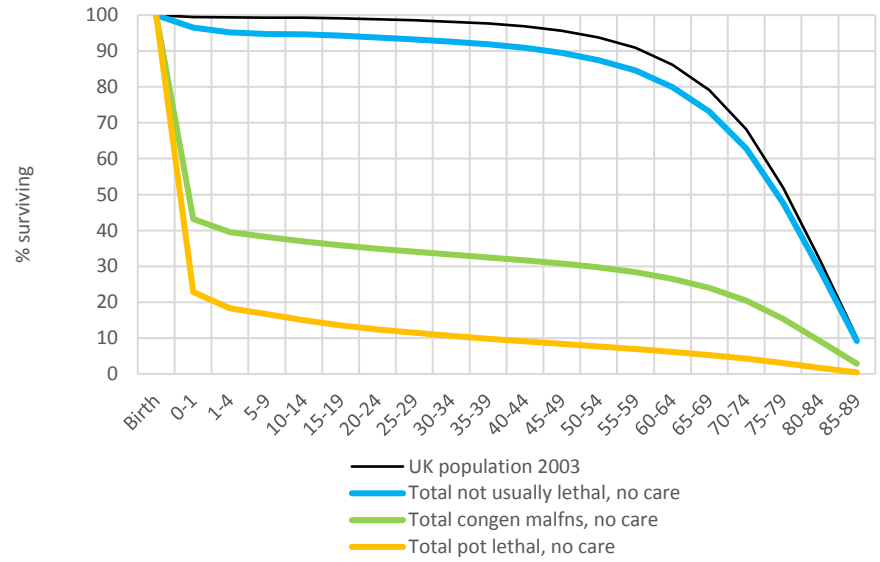

Figure 3.8. Congenital malformations by major severity group. Estimated survival if no care.

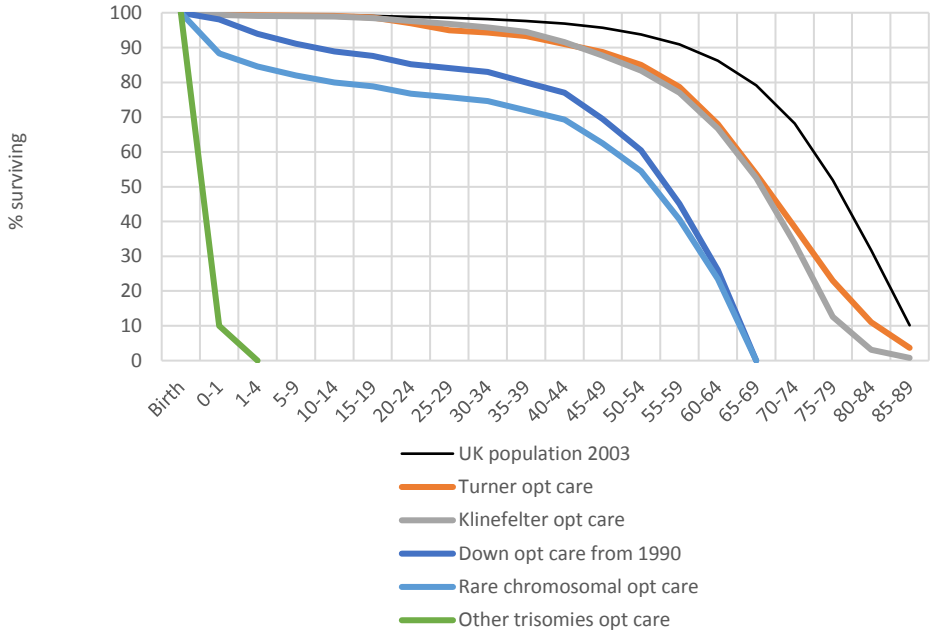

Figure 3.7. Chromosomal disorders. Estimated % survival with optimal care.

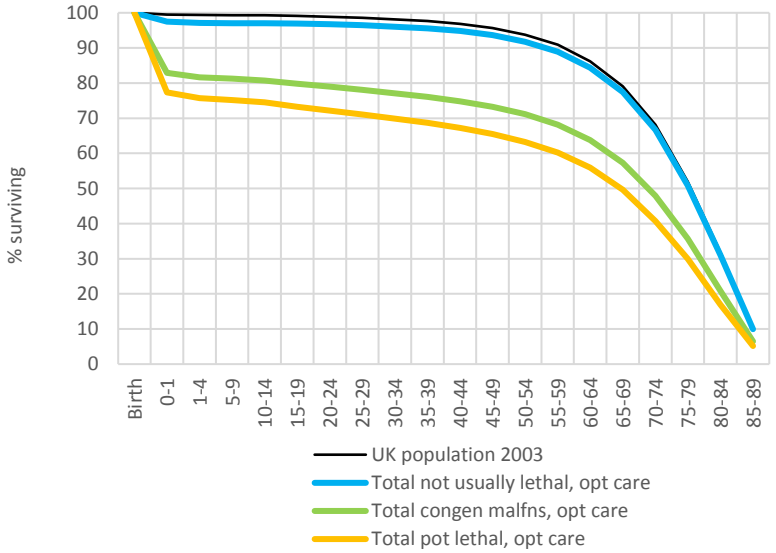

Figure 3.9. Congenital malformations by major severity group. Estimated survival with optimal care

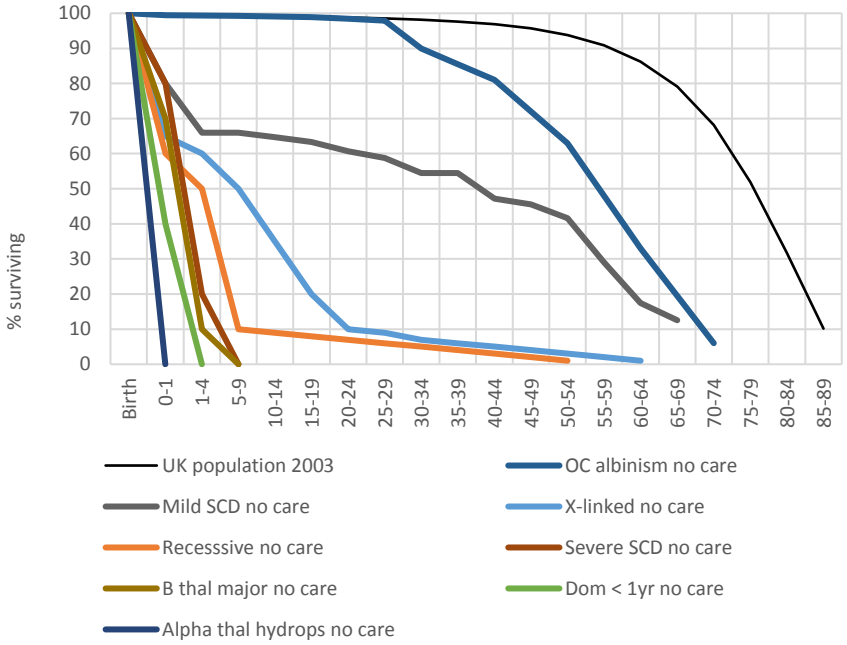

Figure 3.10. Single gene disorders. Estimated % survival with no care. SCD = sickle cell disorder. B thal major = beta thalassaemia major. OC albinism = oculo-cutaneous albinism (in Africa). Dom = dominant.

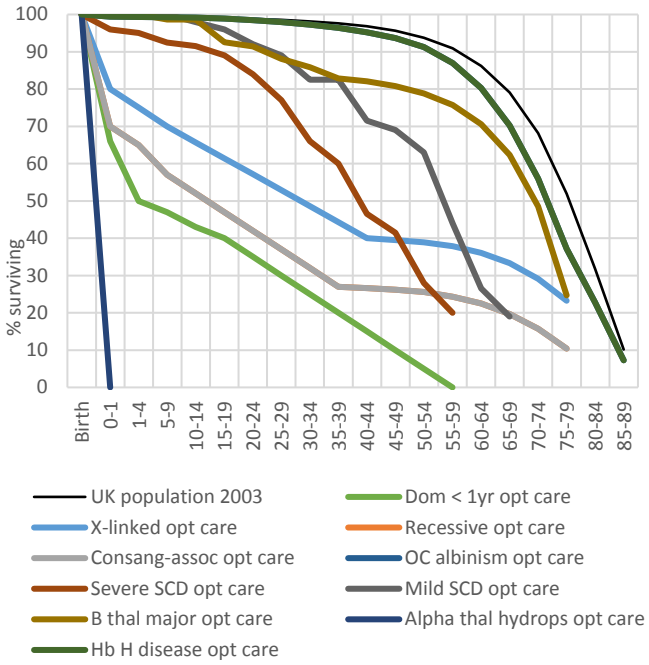

Figure 3.11. Single gene disorders. Estimated survival with optimal care

The above survival curves are *prospective*. They predict future survival, and so long-term age distribution, of the cohort of patients born in a particular year. They do not show patients' current expected age distribution.

Prospective survival curves are used in the following ways for calculating long-term outcomes.

- To estimate disorder-specific *mean life expectancy* (*mean age at death*), with no care and optimal care. These are then combined with estimated access to care to calculate disorder- and country- specific mean life expectancy. This in turn is used to calculate years of life lost, lived cured, or lived with disability.
- For constructing *retrospective survival curves* to use in calculating the number and age distribution of patients living at any given time. For this purpose, estimates for each age group must be adjusted according to the services available at the time they were born. Retrospective survival curves are derived from prospective curves, taking account of the historical evolution of services outlined in Table 3.1.[50]
- For projecting the likely future evolution of patient number and age distribution (a) assuming no policy change and (b) with adoption of specific polices.

[50] Global Database numbers of living patients are calculated from survival with no care and with optimal care, and estimated access to services. Survival with no care does not change over time and access to care is allowed for in all calculations. Therefore the only additional requirement is for estimates of retrospective survival with optimal care, defined as best care available around the time the patients were born.

Table 3.1. Evolution over time of optimal care for congenital disorders, based on Table 2.11 of *Article 2: Core methods for estimates to five years of age*.

	Decade							
Intervention	**1940s**	**1950s**	**1960s**	**1970s**	**1980s**	**1990s**	**2000s**	**2010 -**
Chromosomal disorders		Antibiotics, basic care	Mandatory care			Repair of CHD		
NTD (spina bifida)			Selective closure	routine closure				
Oro-facial clefts	Surgical repair							
Pyloric stenosis	Surgical repair							
Congen heart disease	Repair PDA		Repair "less severe" defects	Cardiac echo	Repair "complex" defects (open heart)		Non-invasive repair	
Limb	Orthopaedics							
Other congen malfns			NN exam: surgical repair			Improved surgical techniques		
Congen hypothyroidism			NN screen, Rx					
Hb: thalassaemia		Antibiotics, basic care	Transfusion, parenteral Fe chelation			Oral iron chelation		
Hb : sickle cell					NN screen & care			
Some metabolic disorders			NN screen, Rx					

Calculation of mean life expectancy

Table 3.2 shows disorder-specific mean life expectancy with no care and optimal care calculated from the full survival curves. The difference between life expectancy with no care and with optimal care measures the survival benefit of care.

Mean life expectancy is used in the Global Database to calculate costs of the disorder, and benefits of interventions, in terms of years of life lost, lived with disability or lived cured.

The rates in Table 3.2 represent life expectancy with the disorder in the absence of any other cause of death. In the Global Database, these “ideal” rates are adjusted by multiplying by local life expectancy divided by a notional optimal life expectancy of 80 years.

Table 3.2. Estimates of mean life expectancy by disorder group, with no care and with optimal care

Main group	Disorder group	Mean life expectancy, years		Years gained per affected person
		No care	Optimal care	
Chromosomal disorders	Down syndrome	7.7	50.6	42.9
	Other trisomies	0.1	0.1	0.0
	Other autosomal	6.9	45.6	38.6
	Turner syndrome	56.8	67.8	11.1
	Klinefelter syndrome	66.4	66.4	0.0
Congenital malformations	Anencephaly	0.0	0.0	0.0
	Spina bifida & e'cele	0.5	41.2	40.7
	Oro-facial clefts	4.4	73.0	68.6
	Very severe CHD	2.0	6.6	4.6
	Severe CHD	15.8	63.6	47.9
	CNS not NTD	0.5	42.5	42.0
	Eye	39.6	74.7	35.0
	Ear, face, neck	72.2	72.2	0.0
	Respiratory	15.6	44.4	28.8
	Digestive system	3.8	60.7	56.9
	Abdominal wall defects	0.5	62.0	61.5
	Urinary system	10.6	67.5	56.9
	Multiple malformations	0.5	29.8	29.3
	Genital system	76.7	76.7	0.0
	Limb	69.8	74.2	4.4
Additional conditions	Congenital hypothyroidism	11.5	80.0	68.5
	Prematurity-associated PDA	30.5	80.0	49.5
	Pyloric stenosis	0.5	80.0	79.5
Rare single gene	Dominant	1.3	17.6	16.3
	X-linked	12.1	39.4	27.3
	Recessive	6.7	28.1	21.4
Consanguinity	Consanguinity-associated	6.7	28.1	21.4
Haemoglobin disorders	Sickle cell disease	3.0	41.5	38.5
	Beta thalassaemia	2.4	65.1	62.7
Genetic risk factors	Rhesus haem disease	1.9	80.0	78.1
	G6PDd kernicterus	1.9	80.0	78.1

Calculation of years of life lost, lived with disability or lived cured

Mean life expectancy for the congenital disorder under consideration can be used to assess the life-time impact of the disorder in terms of years of life lost, and the proportionate outcomes in Table 2.14 of *Article 2: Core methods for estimates to five years of age* can be used to estimate years lived with disability or lived cured. However two values are available for mean life expectancy – “ideal” mean life expectancy in the absence of any other cause of death (see Table 3.2), or life expectancy adjusted for local life expectancy. The Global Database can generate either output. For this presentation mean life expectancy is adjusted for local life expectancy.

The steps in the calculation are then as follows.

1. Calculation of years lost, lived with disability or lived cured, *per affected birth*. The denominator for these calculations is population mean life expectancy.
2. Years of life lost per affected birth are multiplied by annual affected births to obtain implications for the community in terms of total years of life lost, lived with disability or lived cured.
3. These can then be converted to rates using different denominators. For example the GBD calculates years of life lost /year /100,000 population.
4. In the Global Database total years of life affected, years lost, years lived with disability and years lived cured are expressed as years *per individual in the relevant birth cohort*. The method has the advantage of being intuitively accessible to a

general audience (it relates the effect of an intervention to the group that was eligible to receive it), and of having a stable denominator.

All the above calculations are prospective, i.e. predict *future* losses and gains for the relevant birth cohort.

Construction of retrospective survival curves

Curves are constructed in four steps.

1. Define the timing of advances in care for the disorder group under consideration (see table 3.1).
2. Select the "anchor" years from which one wants to look back to estimate the likely number of living patients in that year.
3. Obtain survival data for each phase in the evolution of care. For instance, taking the example of spina bifida, Figure 3.12 shows survival with supportive care only (Laurence and Tew 1971), selective closure for around 30% less severe cases (Lorber and Salfield 1981), and non-selective closure (Mason and Meyers (1986), Oakeshott and Hunt (2003)).

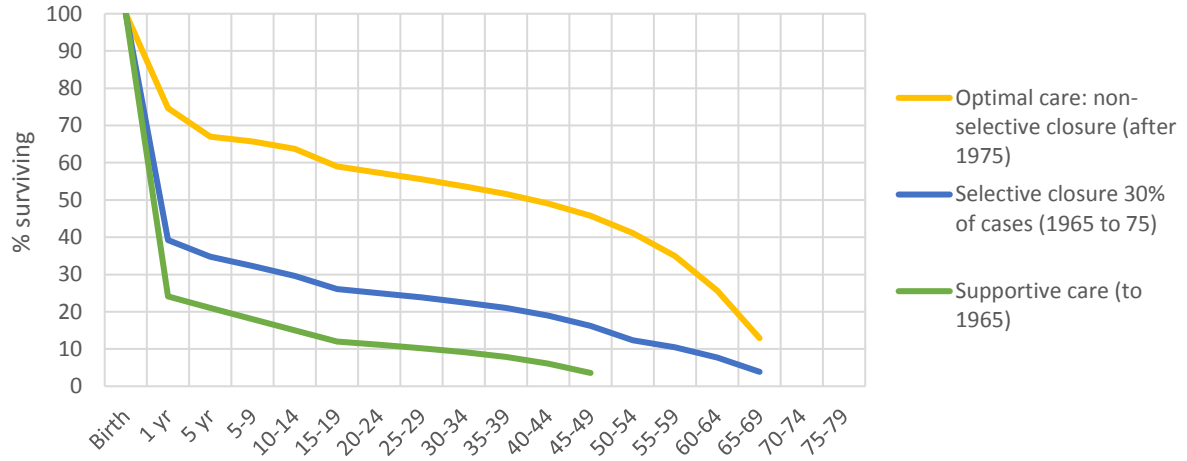

Figure 3.12. Prospective "optimal" survival curves for spina bifida, based on observations at three different periods in the evolution of patient care. The curves show that since non-selective closure only became policy in the later 1970s relatively few survivors over the age of 45 would be expected in 2010, but numbers of older patients are likely to continue rising until 2050. (The number of younger survivors also depends on local policy with respect to prenatal diagnosis (since 1980) and folic acid food fortification (since around 2000)).

4. Construct retrospective survival curves by shifting back sequentially through the prospective curves, as shown in Table 3.3. The first set of columns show prospective survival colour-coded by period. The next six columns show curves for six anchor years spaced at 20 year intervals from 1950 to 2050. This initial calculation assumes abrupt changes in interventions and produces curves with sharp discontinuities. In the last six columns the initial curves are smoothed to allow for the fact that it usually takes 15-20 years for improvements in care to diffuse through an entire health system. (See Annex A5: Creating retrospective survival curves for the full calculation.)

Figure 3.13 shows the smoothed retrospective survival curves. Each curve represents the outcome of "best available care" over the 70 years preceding the anchor year, in terms of the proportion of potential patients in each 5-year age group who are likely to be alive in the anchor year. For example in 2010 one would not expect there to be many survivors with spina bifida over the age of 40, since non-selective closure was only introduced around

1975, and that numbers of older survivors, and service needs, are likely to continue to rise until around 2050 even in settings where prenatal diagnosis is available.

Table 3.3. Prospective and calculated retrospective survival curves for spina bifida with best available care

Age in anchor year	Prospective survival with:			Retrospective survival smoothed					
	Supportive care (to 1965)	Selective closure (1965-75)	Non-selective closure (1975-)	Anchor yr 1950	Anchor yr 1970	Anchor yr 1990	Anchor yr 2010	Anchor yr 2030	Anchor yr 2050
Birth	100	100	100	100	100	100	100	100	100
1 yr	24.1	39.3	74.7	24.1	39.3	74.7	74.7	74.7	74.7
5 yr	21.0	34.8	67.0	21.0	30.7	69.1	69.1	69.1	69.1
5-9	18.0	32.3	65.7	18.0	22.6	65.5	65.5	65.5	65.5
10-14	15.0	29.6	63.7	15.0	15.0	51.8	62.8	62.8	62.8
15-19	12.0	26.1	59.0	12.7	12.7	38.3	60.0	60.0	60.0
20-24	11.1	25.0	57.3	11.1	11.1	20.4	57.3	57.3	57.3
25-29	10.2	23.8	55.6	10.2	10.2	14.8	55.5	55.5	55.5
30-34	9.1	22.5	53.7	9.1	9.1	9.1	43.4	53.6	53.6
35-39	7.9	21.0	51.6	7.7	7.7	7.7	31.2	51.5	51.5
40-44	6.1	19.0	49.1	5.9	5.9	5.9	14.5	48.8	48.8
45-49	3.6	16.2	45.7	3.6	3.6	3.6	3.6	45.3	45.3
50-54		12.3	41.1					32.5	40.6
55-59		10.5	34.9					19.8	33.9
60-64		7.7	25.7					7.7	24.5
65-69		3.9	12.9						12.9
70-74									
75-79									

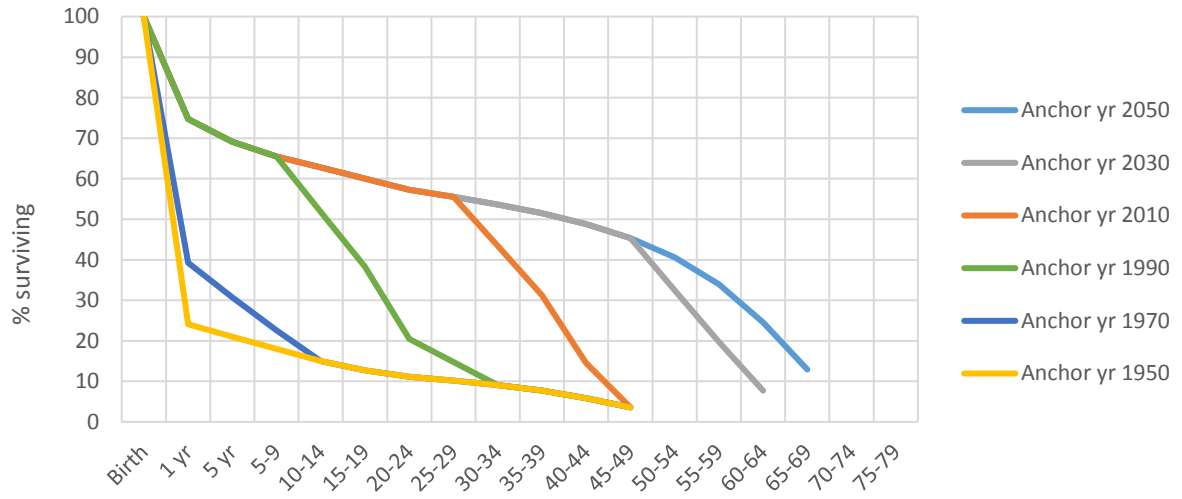

Figure 3.13. Retrospective survival curves for spina bifida, looking back from "anchor years" at 20-year intervals from 1950 to 2050, based on the three curves in Figure 3.7. The curves are smoothed (15-yr rolling averages). Retrospective survival becomes progressively shorter as the anchor year moves back in time.

Calculation of present patient number and age distribution

In order to plan for service needs, policy-makers need to know the approximate numbers presently living with specific disorders. This information can only be reliably obtained using a patient register. However few such registers exist even in high income settings and even for disorders such as Down syndrome, largely because of difficulty in obtaining the necessary long-term (though relatively modest) funding. Therefore, for most countries, it is necessary to devise a method for estimating present patient numbers and age distribution. In the Global Database this is achieved for each disorder group using the following steps.

1. Obtain data on the number and age distribution of the relevant population in the year (or 5-year period) for which the information is required, in thousands by 5-year age

intervals. World Population Prospects[51] (WPP) provides country-specific estimates by 5-year interval from 1950-2100.

2. Apply the baseline *live birth* prevalence of the disorder to calculate the number of patients who would be living in the year of interest by 5-year age intervals, if their survival equalled the population norm.
3. Use available data on the evolution of the effect of interventions before birth by 5-year age intervals, to calculate (a) the number of affected births avoided and (b) potential actual patient number if survival equalled the population norm, in each 5-year age group.
4. Calculate estimated access to services by 5-year age group, using WPP historical infant mortality rates.
5. Calculate (a) the number of surviving patients by 5-year age interval, and (b) the number in each 5-year age group who died at earlier ages, using disorder-specific long-term survival curves with optimal care and no care and estimated access to services.

Note that it is not necessary to adjust any of these estimates for local mortality, because when the denominator is number surviving in each age group, all-cause death is already taken into account.

Estimation of past and future patient numbers

Thanks to the availability of WPP demographic data, the same method can be used to estimate the number and age distribution of living patients at different periods in the past from 1950 onwards. It can also be used project patient numbers and age distribution by 5 year intervals up to 2050.

Future projections of the likely effects of implementing interventions such as folic acid food fortification or prenatal diagnosis with the option of termination of pregnancy are of particular interest to policy-makers. They can be calculated (a) assuming no change in present policies, and (b) assuming world-wide spread of available interventions. In the Global Database all future projections allow for changes in estimated access to services.

Long-term outputs

Long-term outputs from the Global Database include (1) Estimated years of life lost, lived with disability or lived cured. (2) Estimated number and age distribution of living affected individuals. (2) Projected future effects on numbers and outcomes, of present policies, and potential policy changes. (3) Improved assessment of long-term costs and benefits.

Estimated years of life lost, lived with disability or cured

An initial approach to quantifying the burden of a disorder is calculation of years of life lost or lived with disability due to the disorder, as used in the Global Burden of Disease Study (GBD). In addition, the Global Database includes calculation of years of life gained and/or lived cured due to interventions.

Years affected per person born is the same as local mean life expectancy. This provides the envelope for all estimates of outcomes. Figure 3.14 shows Global Database estimates for total months affected by constitutional congenital disorders per person in the 2010-14 birth cohort, with outcomes in the absence of intervention. The world average is more than 27

[51] http://esa.un.org/unpd/wpp

months affected per person born. In the absence of intervention these disorders would be responsible for loss of 20 months of life per person born.

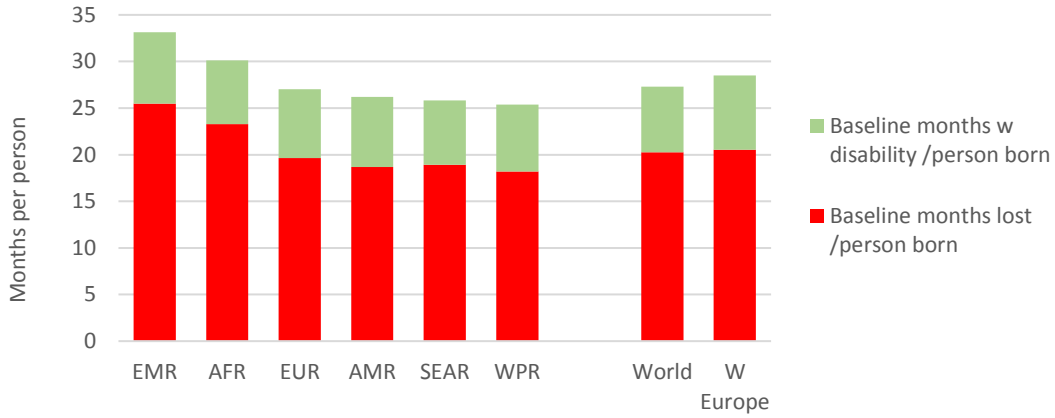

Figure 3.14. Total constitutional congenital disorders: live births only. Estimated baseline months affected /person born, by WHO region ranked in descending order of total months affected. The column heights show baseline months affected per individual in the birth cohort, adjusted to local life expectancy.

Figure 3.15 shows estimated actual outcomes in 2020-14, in terms of months of life lost, lived with disability or lived cured per person born. The striking reduction in death and disability in Western Europe demonstrates the potential of global implementation of interventions for congenital disorders.

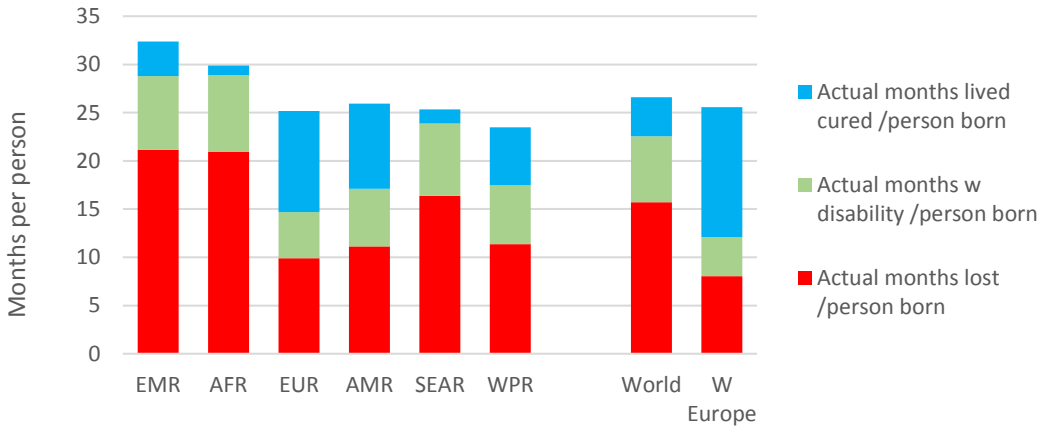

Figure 3.15. Total constitutional congenital disorders, live births only. Estimated actual outcomes 2010-14, expressed as years of life lost, lived with disability or lived cured per person in the relevant birth cohort, by WHO region.

Table 3.4 shows the proportionate change in outcomes by WHO region. The row for Western Europe shows the maximum present effect of interventions (except folic acid food fortification). It shows nearly 50% of years affected are lived cured, 11% lived with disability, and around 20% of affected years lost, and 21% reduction in years actually affected due to interventions before birth.

Table 3.4. Estimated years per person born affected by congenital disorders, and proportion with different outcomes in the absence of care and in 2005-09 by WHO region

WHO region	Years affected /person	Outcomes, % of years affected /person					
		No care (baseline)		Estimated actual outcomes 2005-09			
		Potential yrs life lost	Potential yrs lived w disability	Reduction in yrs affected	Years of life lost	Years lived w disability	Years lived cured
AFR	2.45	81.2	18.8	1.6	75.1	21.6	1.6
AMR	2.49	79.1	20.9	10.4	40.2	20.5	28.9
EMR	3.27	82.9	17.1	4.0	66.7	21.4	8.3
EUR	2.5	79.6	20.4	16.0	29.6	16.0	38.4
SEAR	2.36	78.4	22.0	2.5	66.9	23.7	6.8
WPR	2.21	75.6	24.4	7.2	44.3	20.8	27.6
World	2.52	79.0	21.0	5.2	57.1	24.6	13.1
W. Europe	2.68	79.9	19.8	21.3	19.8	10.8	48.1

Estimated number and age distribution of living patients

Since WPP provides age distribution data from 1950 onwards, it is possible to generate estimates of the number and age distribution of patients living in any year from 1950 to 2015 in any country. The method generates the following estimates for each disorder, and provides a comprehensive picture of the history of the selected disorder up to the chosen year.

- Potential number and age distribution if survival equalled the population norm
- Affected births avoided by interventions
- Deaths due to lack of access to care available at the time
- "Unavoidable deaths" that would have occurred with best available care
- Number and age distribution of patients living with disability or effectively cured.
- Annual deaths due to the disorder, and their age distribution (by applying prospective survival curves to estimated living patients).

Since the data is complex it is best presented in charts. As an example, Figure 3.16 shows global estimates for spina bifida by 5-year age intervals in 2010.

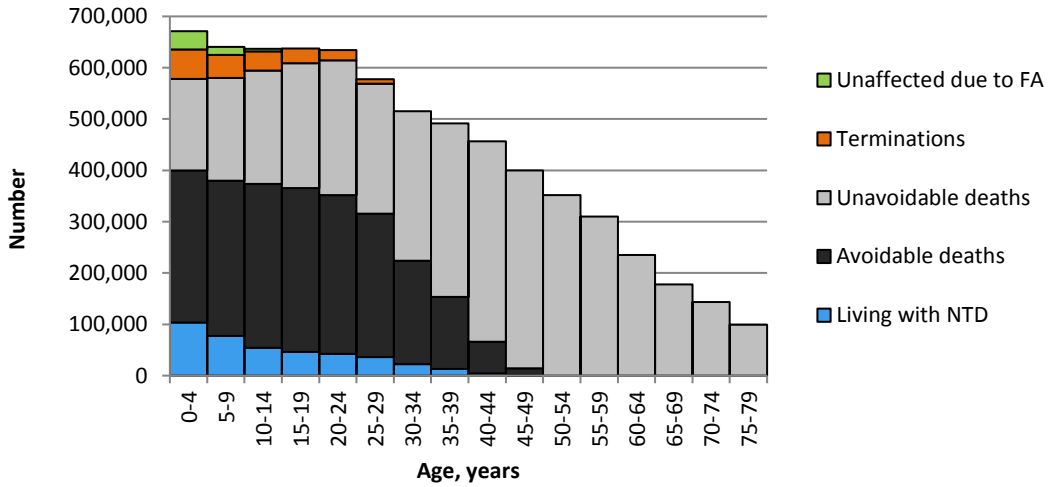

Figure 3.16. World 2010. Estimated distribution of outcomes for spina bifida in 2010. The total outline represents the number who would be living with spina bifida if survival equalled the population norm (6,977,400).

In Figure 3.16 (world estimates for spina bifida):

- The total outline shows the number of individuals who would be living with spina bifida if survival equalled the population norm, according to age in 2010 (6.98 million). The outline reflects the age distribution of the world population in 2010.
- The green fill shows cases avoided by folic acid food fortification (only 56 thousand in 2010 because fortification only started to become policy in the late 1990s).
- The orange fill shows cases avoided by termination of pregnancy (196 thousand in 2010).
- The grey fill shows deaths that would have occurred even with best care available when the affected person was born (unavoidable deaths). The great majority of deaths occurred soon after birth, but they appear in all age groups because the chart shows all outcomes. The black fill shows numbers of deaths that occurred because of lack of access to available care (avoidable deaths). (Total losses from the current world population due to spina bifida = 6.35 million).
- The blue fill shows estimated numbers living with spina bifida in 2010 (399 thousand).

Future projections

Figures 3.17 and 3.18 show global projections for spina bifida in 2050 with two extreme policy assumptions: (a) no change in present policies on folic acid food fortification and abortion for fetal impairment, and (b) both global spread of folic acid food fortification and unrestricted access to prenatal diagnosis with the option of termination of pregnancy for those with access to services from the year 2010.

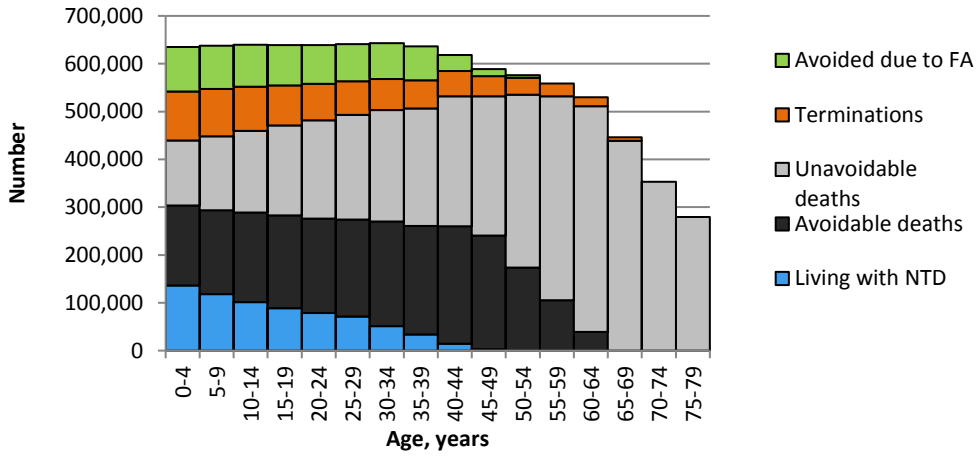

Figure 3.17. World 2050. Estimated distribution of outcomes for potential spina bifida if no change in present policies. Estimated total unaffected due to folic acid food fortification = 714 thousand; total avoided due to termination of pregnancy = 832 thousand. Total deaths 7.2 million. Total living with spina bifida = 696 thousand.

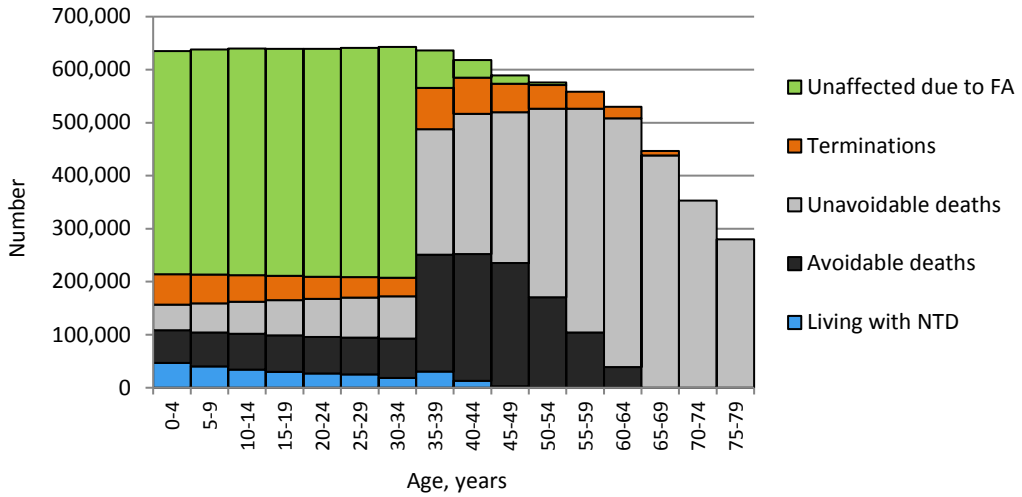

Figure 3.18. World 2050. Estimated distribution of outcomes of potential spina bifida, if global FA food fortification and global legalisation of termination of pregnancy for fetal impairment, from 2010. Estimated total unaffected due to folic acid food fortification = 3.12 million; total avoided due to termination of pregnancy = 442 thousand. Total deaths 5.22 million. Total living with spina bifida = 268 thousand.

Table 3.5 summarises the estimated long-term effects of different policy decisions for spina bifida at a global level. All the estimates take account of change in access to care in the time period involved.

Table 3.5. World picture of spina bifida: past, and potential future numbers with different future scenarios

Estimate	Past history				Future: from 2010					
					no policy change		global FA fortification		global FA and TOP legal	
	1950	1970	1990	2010	2030	2050	2030	2050	2030	2050
Potential if no intervention	2,532	3,614	5,231	6,977	8,324	8,324	8,324	9,062	9,062	9,062
Unaffected due to FA	0	0	0	56	370	714	1,839	3,123	1,839	3,123
Termination of pregnancy	0	0	28	196	476	832	294	442	393	629
Potential with interventions	2,532	3,614	5,203	6,725	7,477	7,516	6,190	5,496	6,091	5,310
Total deaths	2,486	3,490	4,989	6,347	7,085	7,224	5,946	5,412	5,858	5,218
Living with NTD	47	124	207	399	545	696	327	324	297	268
% of potential unaffected due to FA				0.8	4.5	7.9	22.1	34.5	22.1	34.5
% of potential avoided by TOP			0.5	2.8	5.7	9.2	3.5	4.9	4.7	6.9
% of potential living with NTD	1.8	3.4	4.0	5.9	7.3	9.3	5.3	5.9	4.9	5.1

Discussion

Additional inputs and stages

Extending survival curves

For long-term estimates it is necessary to extend the existing observation-based optimal survival curves

Life-time data on survival with congenital disorders is necessary to generate long-term estimates, but most existing data only applies for survival to 20-30 years of age. This is because many of the interventions that increase survival were introduced between 1950 and 1980, and follow-up observation for at least 50 years would be required to evaluate their full effect. Therefore in many cases it is necessary to extrapolate from existing survival data to obtain a full life-time curve. In the Global Database this is done in two ways, (a) based on the observed excess attrition in the oldest surviving group plus the population rate, and (b) assuming the population rate for all survivors after 20 years of age.

In fact, because the highest loss of life is in the first five years, uncertainty in extrapolation to older age groups has relatively little effect on estimated life expectancy (Table 3.6). It

therefore has relatively little effect on most estimates of years of life lost due to congenital disorders.

Table 3.6. Comparison of mean life expectancy calculated based on survival curves to 20 years extrapolated in two ways. Calculations based on Tennant, Pearce *et al.* (2010) adjusted for effect of TOP

Disorder group	Disorder-specific attrition rate plus population rate	Population attrition rate alone	Difference, years
Neural tube defects	41.2	47.3	6.2
CNS not NTD	42.5	48.2	5.7
Multiple malformations	29.8	33.8	4.1
Cardiovascular system	65.8	68.6	2.7
Digestive system	60.7	63.1	2.4
Eye	74.7	74.7	0
Ear, face, and neck	72.2	72.2	0
Respiratory	44.4	44.4	0
Orofacial clefts	75.6	75.6	0
Abdominal wall	62	62	0
Urinary	67.5	67.5	0
Genital	76.7	76.7	0
Limb	74.2	74.2	0
UK population 2003	76.7	76.7	0

Calculating number and age distribution of surviving patients

The Global Database uses current population age distribution as the basis for calculating the "baseline" (potential) number of living patients, i.e. the number who would be alive if their survival had equalled the population norm. Since the number of in each 5-year group of the general population is the product of births in that interval minus all antecedent deaths from all causes, it is not necessary to seek other information on numbers of births or survival.

Retrospective survival curves are then applied, to estimate the number of patients actually surviving in each age group. There are several sources of uncertainty in the calculation and application of the retrospective curves (see *Article 6: Chromosomal disorders: calculating birth prevalence, survival and patient numbers* for an example). Firstly, observational data on survival in high income settings before 1970 is scanty. Secondly, the curves currently used assume prompt and equitable implementation of advances as they became available, but this is unlikely to have been the case: it usually takes 10-20 years for validated interventions to penetrate an entire health system. Therefore in some cases numbers of older survivors may be over-estimated.

Calculating age distribution at death

Mean life expectancy enables calculation of years of life lost, but does not give any information on distribution of age at death. This can only be calculated from estimated patient number and age distribution. Distribution of age at death is important, because it enables informative comparison with age at death estimates produced by the Global Burden of Disease study.

Previous studies

The only previous study explicitly designed to assess burden of congenital anomalies remains that of Czeizel and Sankaranarayanan (1984), who not only recorded birth prevalence but also collected follow-up data on infant mortality and survival to 20 years of age, categorised types of disability in survivors, and expressed results in terms of years of life lost, lived with disability or lived effectively cured. The published results are summarised in Table 3.7. This remarkable study passed almost unnoticed internationally because its global relevance was not recognised.

In Hungary mean life expectancy was 70 years when Czeizel and Sankaranarayanan (1984) made their classical estimates of burden. Their estimates would need to be adjusted to contemporary mean life expectancy for comparison with Global Database estimates.

Later reports from Skjaerven, Wilcox *et al.* (1999) and Lie, Wilcox *et al.* (2001), who collected data on Swedish people born with congenital anomalies in order to assess their genetic contribution to subsequent generations, have added valuable diagnostic-group-specific data on long-term survival and reproductive success.

Table 3.7. Czeizel and Sankaranarayanan (1984) estimates of average years of life affected per person in the birth cohort, calculated on an average life expectancy of 70 years

System affected	Affected births /1,000 LB	Average years of life per person born			
		Total years affected by congenital. anomaly	Average years lost	Average years lived with disability	Average years lived cured
Central nervous system	2.17	0.152	0.119	0.029	0.004
Eye	0.32	0.022	0.004	0.010	0.008
Ear, face, neck	0.46	0.032	0.000	0.010	0.023
Cardiovascular system	7.92	0.554	0.184	0.098	0.274
Respiratory system	0.28	0.020	0.007	0.007	0.006
Cleft palate, or lip & palate	1.42	0.099	0.003	0.022	0.076
Alimentary system	2.78	0.195	0.043	0.007	0.144
Urinary system	1.57	0.110	0.021	0.040	0.049
Skeletal system	2.07	0.145	0.027	0.027	0.091
Miscellaneous including multiple	2.74	0.192	0.043	0.039	0.109
Total potentially lethal	21.73	1.52	0.45	0.29	0.78
Musculo-skeletal system	5.43	0.380	0.000	0.012	0.513
Genital organs	7.52	0.526	0.000	0.072	0.454
Total not usually lethal	12.95	0.91	0.00	0.08	0.97
Total non-chromosomal	**34.68**	**2.43**	**0.45**	**0.37**	**1.75**
Total chromosomal	1.26	0.088	0.031	0.056	0.001
Total	**35.94**	**2.66**	**0.48**	**0.43**	**1.75**

Musculo-skeletal system: Western European rate for congenital dislocation of the hip are used, instead of the unusually high Hungarian rate.

Improving the assessment of costs and benefits

For a more general discussion of this topic, and the limitations of present methods, see Annex A7: Assessing costs and benefits.

In their classical study of the burden of congenital anomalies Czeizel and Sankaranarayanan (1984) recognised the limitations of an approach limited to assessing death, disability and cure. As a step towards a more refined quantification of disability they initiated a classification of types of disability. However they made no attempt at quantification in view of the following serious limitations.

1. The examples considered apply only for congenital anomalies. To extend the approach to other congenital disorders it would be necessary to create many new categories, in combinations specific to each diagnosis.[52]. Furthermore, differences between the implications of different clinical problems makes it almost impossible to derive a meaningful total score for comparative purposes.[53]
2. The approach focuses almost entirely on physical disability. However the predominant challenge in the unfolding life of people born with a congenital disorder is social - the possibility of integration into society.
3. There is no allowance for effects on the family. For example, rhesus haemolytic disease and alpha thalassaemia hydrops fetalis involve a serious risk to the life of the mother: most single gene disorders have a high recurrence risk and so reduce the

[52] For example, kernicterus due to G6PD deficiency or rhesus incompatibility, functional disability due to neuro-degenerative disorders, anaemia and pain due to haemoglobin disorders.
[53] The Global Burden of Disease study tries to overcome this problem by using rating panels to assign relative disability weights, and thus to calculate disability-adjusted life years (DALYs) for each clinical picture.

parents' reproductive success, and entrain a quantifiable risk for relatives of having similarly-affected children.

Developing a truly sensitive approach for the full range of congenital disorders, though worthwhile, would take considerable time and effort, starting with agreement on common quantitative methods.

As an interim step towards improving the assessment of disability, a generic approach that can be applied to any childhood-onset disorder might be developed by shifting the primary focus from clinical measures to factors affecting social integration (see Annex A6: The need for better quantitative methods for assessing the burden of congenital disorders*)*. The social approach would take account of an affected individual's ability to reach adulthood and achieve normal life-time goals such as ability to live independently, sexual development and functioning, and ability to build a family. In the Global Database success in building a family – reproductive success – is taken as the single most important quantifiable indicator of the ultimate effectiveness of current interventions.[54] Interestingly, reproductive success is the same as genetic fitness[55] as defined in classical population genetics – the ability of an individual to pass their genes on to the next generation, relative to the population norm (Harris (1970), Bodmer and Cavalli-Sforza (1976)).

Reproductive success has the advantage of being measurable. In a study designed to assess the extent to which improving the care of individuals with congenital anomalies affects the human gene pool, Skjaerven, Wilcox *et al.* (1999) and Lie, Wilcox *et al.* (2001) documented survival and reproduction to age 30 of affected individuals born in Norway in 1967-1982 (see *Annex A6: The need for better quantitative methods for assessing the burden of congenital disorders* for fuller description). Table 3.8 shows estimates of the proportion of infants with the disabilities included in the Global Database expected to reach 20 years of age at the present time, and the per cent of these survivors expected to be able to build a family with no care and with optimal care. The table combines the estimates of Skjaerevan and Lie for congenital anomalies[56], with additional data from the literature or based on the clinical picture of each disorder. The table incidentally underlines the inadequacy of a purely physical approach by demonstrating the difference between survival and ability to build a family.

Note: The current Global Database does not produce estimates for reproductive success, however we anticipate that this will be included in the next version of the Global Database.

[54] This means that the ultimate aim of treatment is to restore genetic fitness to patients – a point for discussion.
[55] The term reproductive success, which has the same meaning, is preferable for a general audience.
[56] For this table, an attempt is made to allow for the fact that Skjaerevan and Lie did not provide estimates for all disorder groups, their observations apply only for a high income setting, and some rates are now probably under-estimates because their data applies for individuals born between 1967 and 1982, but treatment, public attitudes to disability, and availability of social support have all improved subsequently.

Table 3.8. Estimated proportion of survivors to adult life able to achieve main life objectives

Main group	Disorder group	Potential) live births /1,000	No care		Optimal care	
			% surviving @ 20 yr	Ability of survivors to build a family, % of pop norm	% surviving @ 20 yr	Ability of survivors to build a family, % of pop norm
Chromosomal disorders	Down syndrome (+21)	1.59	18.5	0	91	0
	Other trisomies (+13, +18)	0.311	0	0	0	0
	Other autosomal	0.55	10	0	49	0
	Turner syndrome (XO)	0.175	94	0	97	19
	Klinefelter syndrome (XXY)	0.7	98	0	98	14
Isolated congenital malformations	Anencephaly	0.51	0	0	0	0
	Spina bifida & e'cele	1.02	0	0	57	31
	Oro-facial clefts	0.91	2.5	13	98	71
	Very severe CHD	0.38	3.1	0	13	31
	Severe CHD	1.13	39.6	0	76	31
	Less severe CHD	1.79	26.1	15	98	100
	CNS not NTD	0.84	0	0	61	14
	Eye	0.27	56.2	25	96	77
	Ear, face, neck	0.27	93.1	25	93	68
	Respiratory system	0.46	23.8	25	57	65
	Digestive system	0.95	4.3	25	81	64
	Abdominal wall defects	0.33	0	0	80	57
	Urinary system	2.56	16.5	45	87	84
	Multiple malformations	1.33	0	0	43	23
	Genital system	1.76	98.8	25	100	56
	Limb	3.39	91.2	50	96	66
Additional conditions	Congenital hypothyroidism	0.21	0	0	100	100
	PDA assoc w prematurity	0.3	12	0	100	100
	Pyloric stenosis	0.87	0	0	100	100
Single gene disorders	Dominant (onset <1 yr)	1.4	0	0	35	15
	X-linked	0.05	10	13	57	12
	Recessive (baseline)	1.66	7	3	42	13
	Consang-assoc recessives	4.31	7	3	42	13
	Severe SCD	2.09	0	0	84	40
	Mild SCD	0.72	60.7	61	92	46
	Transfusion-dependent b thal	0.23	0	0	91	45
	Milder b thal & Hb H disease	0.16	60.7	61	99	49
	Apha thal hydrops fetalis	0.016	0	0	0	0
Genetic risk factors	Rhesus haem disease	0.9	0	0	100	100
	G6PDd kernicterus	1.3	0	0	100	100

Article 4: Uses of demographic and geographic data

Abstract

Demographic data provides an essential background for Community Genetics. It is not only essential for epidemiological estimates, but also provides an overall picture of the evolution of the health status of a population. This article amplifies the summary of demographic data given in *Article 2: Core methods for estimates to five years of age*.

Demographic data used in the Global Database is obtained from the following sources.

1. Basic demographic data from UN World Population Prospects 2015 revision: country estimates from 1950-2015, and median projections from 2015-2050, for: total population; annual live births; infant mortality; under-5 mortality; mean life expectancy (both sexes); total fertility rate; sex ratio at birth; per cent of births to mothers aged 35 plus; and population age and sex distribution.
2. Stillbirths: from the systematic review of Cousens et al. 2011.
3. Neonatal mortality: from www.childmortality.org
4. Coefficient of consanguinity: from publications by and personal communications with A. Bittles, and www.consang.net
5. Early mortality due to HIV/AIDS, from IHME-GBD 2013

Charts are included to illustrate the evolution of each demographic indicator from 1950 to 2015, and median projections to 2050.

The article comments on the general relevance of each indicator, points out potential pitfalls in its direct application to the epidemiology of congenital disorders, and details the way it is applied in the Global Database.

Article 5: Estimating access to services

Abstract

This article gives details of the method for estimating access to services outlined in *Article 2: Core methods for estimates to five years of age.*

The two General Method articles show that enough information exists to enable country-specific estimates of the baseline birth prevalence of constitutional congenital disorders country, and outcomes in the absence of care and with optimal care. Therefore if the proportion of the population with access to optimal care is known, it is possible to construct a provisional picture of annual affected births and outcomes. However there is no single readily-available source of global information on access to care, so was necessary to develop a general method for estimating access.

A first step towards a general method was taken when the WHO Child Health Epidemiology Reference Group (CHERG) defined five levels of access based on neonatal mortality rate. This article describes how this initial step was built on to develop an equation for estimating the proportion of a population with access to optimal care, based on infant mortality (IMR).

Proportion with access = (1-BETADIST(LN(IMR-10),2.5,5.5,0,LN(1000)))

However a problem of circularity arises with use of this equation because early-onset congenital disorders themselves contribute significantly to infant mortality. Therefore before being used as a basis for estimating access, infant mortality should be adjusted for mortality due to congenital disorders whose baseline birth prevalence differs substantially between populations. Accordingly in the Global Database access is estimated on the basis of infant mortality minus estimated mortality due to consanguinity-related disorders and AIDS. Adjustment for mortality due to haemoglobin disorders was also considered, but not implemented for reasons given in the article.

The article also describes how estimates for termination of pregnancy are adjusted according to the local legality or otherwise of abortion for fetal impairment.

The article emphasises the provisional nature of all estimates of access. Ideally an alternative method of estimating access in the case of constitutional congenital disorders, may be by comparing Global Database estimates of actual live birth prevalence with the recorded number of cases treated, or with utilisation of essentials including blood, blood products, and pharmaceuticals.

Part II. Congenital anomalies

Article 6: Chromosomal disorders: calculating birth prevalence, survival and patient numbers

Abstract

This article gives details of the methods used to obtain the estimates of birth prevalence and outcomes for chromosomal disorders presented in the General Method articles.

Chromosomal disorders have two characteristics that are particularly helpful in estimating their global epidemiology. Firstly, the baseline birth prevalence of Down syndrome and other trisomies can be calculated from maternal age distribution, providing independent estimates that can be compared with registry data. Secondly, full life-time survival data is available for the major groups of chromosomal disorder.

Additional input data needed for estimates of chromosomal disorders are: (1) UN World Population Prospects (WPP) estimates of maternal age distribution from 1950-2015, and median projections to 2050; (2) UN Demographic Yearbook data on accuracy of age reporting and "age heaping"; (3) EUROCAT and ICBDSR data on reported birth prevalence of chromosomal disorders, and pregnancy outcomes; (4) updated estimates of maternal-age-related Down syndrome birth prevalence, and birth prevalence of other chromosomal disorders.

Calculation of Down syndrome birth prevalence using demographic data required the following steps.

(1) Calculation of Down syndrome live birth prevalence by *5-year maternal age intervals*, to match the age intervals used in demographic databases.

(2) Application of these rates to WPP maternal age distributions: this gave improbably high rates for many lower-income countries, almost certainly due to inaccuracy of age data as shown by UN data on "*age heaping*".

(3) It was observed that when only maternal age data from countries with demonstrably reliable age reporting is used, there is a linear relationship between estimate Down syndrome live birth rate based on the full range of maternal age, and the per cent of mothers 35 plus, described by the following simple equation.

Down potential live births /1,000 = 0.834 + (% of mothers 35plus x 0.067) +/- 4.2%.

In the Global Database (a) this equation is used to calculate Down syndrome live birth prevalence; (b) the baseline live birth prevalence of "other trisomies" (Edwards syndrome plus Patau syndrome) is calculated as 19.5% of Down syndrome; (c) The baseline live birth prevalences of other chromosomal disorders are considered to be constant and unrelated to maternal age; (d) total affected birth prevalences (stillbirths plus live births) are calculated from live birth prevalences by adding known (or estimated) rates for fetal death/stillbirth.

A detailed comparison with Down syndrome birth prevalences and pregnancy outcomes in the EUROCAT and ICBDSR "umbrella" congenital anomaly registries supports the general applicability of the simplified maternal-age-based estimates.

These inputs are used to estimate early mortality, mean life expectancy, number of affected individuals living at any one time, and years of life affected, and lost or lived with disability due to chromosomal disorders. The following tables give an overall summary to 5 years of age for total chromosomal disorders in 2010 by WHO region, including estimates of the per cent decrease in pathological outcomes due to current interventions. A negative value in the final column indicates an increase in survivors with disability at age 5. Table 6.3 shows long-term estimates in terms of the number of months affected by chromosomal disorders per person born in 2010.

Table 6.1. Total chromosomal disorders. Estimated potential and actual stillbirths by WHO region.

WHO region	Potential total SB & LB /1,000	Potential stillbirths /1,000	Stillbirths /1,000 avoided by TOP	Actual stillbirths /1,000	% of stillbirths avoided by TOP
AFR	4.40	0.76	0.02	0.74	3.2
AMR	4.11	0.70	0.12	0.58	17.8
EMR	4.33	0.75	0.06	0.68	8.4
EUR	4.31	0.74	0.37	0.37	49.8
SEAR	3.70	0.62	0.05	0.58	7.5
WPR	3.66	0.62	0.19	0.42	31.3
World	4.02	0.69	0.11	0.58	15.4
W Europe	5.05	0.89	0.61	0.28	68.8

Table 6.2. Total chromosomal disorders. Estimated potential and actual affected live birth prevalence and outcomes in 2010 by WHO region

WHO region	Potential LB /1,000	Potential under-5 deaths /1,000	Potential living @ 5 yr w disabil	% reduction LB due to TOP	Actual live births /1,000	% of LB with access to care	Actual under-5 deaths /1,000	Actual living @ 5 yr w disabil /1,000	% reduction in under-5 deaths	% reduction in disability at 5 yr
AFR	3.64	1.99	1.38	0.7	3.62	5.6	1.86	1.44	6.6	-4.4
AMR	3.40	1.88	1.48	10.1	3.06	59.4	0.96	2.04	48.7	-37.8
EMR	3.59	1.99	1.47	3.4	3.46	25.4	1.57	1.73	20.9	-17.7
EUR	3.57	2.00	1.53	32.4	2.41	79.8	0.51	1.87	74.6	-21.8
SEAR	3.08	1.62	1.35	2.9	2.99	14.7	1.39	1.47	14.3	-8.6
WPR	3.04	1.61	1.39	17.1	2.52	50.6	0.83	1.64	48.4	-18.1
World	3.34	1.80	1.41	8.2	3.06	28.5	1.29	1.62	28.5	-15.3
W Europe	4.16	2.45	1.70	49.9	2.09	100.0	0.17	1.90	92.9	-11.8

Table 6.3. Total chromosomal disorders: live births. Estimated potential and actual months affected by chromosomal disorders per person born

WHO region	Potential, if no intervention			Actual with current interventions			% reduction in 2010 in:		
	Average months affected	Months of life lost	Months lived w disability	Months avoided by TOP	Months of life lost	Months lived w disability	Months actually affected	Months of life lost	Months lived w disability
AFR	2.39	1.70	0.68	0.02	1.52	0.85	0.7	10.5	-23.8
AMR	3.10	2.25	0.85	0.42	1.50	1.27	10.4	33.3	-50.7
EMR	2.90	2.11	0.79	0.15	1.45	1.35	3.6	31.3	-70.5
EUR	3.25	2.40	0.85	1.44	1.20	0.96	33.8	50.1	-12.0
SEAR	2.48	1.73	0.75	0.10	1.05	1.36	3.0	39.5	-82.0
WPR	2.74	1.93	0.81	0.65	0.93	1.32	17.7	51.7	-63.2
World	2.69	1.92	0.77	0.34	1.25	1.19	9.4	35.1	-54.8
W Europe	4.07	3.12	0.95	2.61	1.09	0.95	49.9	65.1	0.2

Article 7: Congenital malformations: birth prevalence and birth outcomes

Abstract

This article gives details of the methods used to obtain the estimates of birth prevalence and outcomes to age five for congenital malformations shown in the General Method articles. To simplify presentation the topic is sub-divided into a main article describing the general method used for congenital malformations, and four subsidiary articles describing how estimates are obtained for neural tube defects, oro-facial clefts, congenital heart disease, and three additional conditions not usually included in congenital anomaly registries. This summary covers all except the last of these articles.

EUROCAT and ICBDSR umbrella registry data on congenital malformations is used in the Global Database for three main purposes.

1. To enter reported baseline (potential) birth prevalences in participating countries.
2. To follow changes with time in the distribution of birth outcomes (termination of pregnancy for fetal impairment, fetal death/stillbirth, live birth) in participating countries.
3. To obtain average European rates for birth prevalences and outcomes that can be used for generating estimates for countries with little or no observational data.

Both ICBDSR and EUROCAT data are used for the first two purposes, but only the comprehensive EUROCAT data can be used to derive average European rates for the full range of congenital malformations. The article includes close examination of the strengths and limitations of EUROCAT data.

Next it shows how EUROCAT data for non-syndromic congenital malformations are adjusted for associations to obtain rates for isolated malformations by system group, and for multiple malformations. The adjustment needed for rates for outcomes differ by malformation group.

Then there are separate sections on individual malformation groups

- Neural tube defects: country and regional differences in baseline birth prevalence, calculation of rates for termination of pregnancy, effects of folic acid food fortification.
- Oro-facial clefts. Variation in birth prevalence - ? role of under-ascertainment.
- Congenital heart disease. The distinction between congenital heart defects (6-8/1,000 births) and congenital heart disease. No evidence of major differences between populations though there may be a consanguinity-related increase. Bundled into 3 (or two?) main groups. Effect of PND on birth prevalence of most severe and lethal disorders.

The following tables give an overall summary of prevalence and outcomes to 5 years of age for total congenital malformations in 2010 by WHO region. The tables include estimates of the per cent reduction of pathological outcomes due to current interventions. A negative value indicates an increase in survivors with disability at age 5.

Table 7.1. Total congenital malformations. Estimated potential and actual stillbirths by WHO region.

WHO region	Potential total births /1,000	Potential stillbirths /1,000	Stillbirths /1,000 avoided by FAFF & TOP	Actual stillbirths /1,000	% of stillbirths avoided by FAFF & TOP
AFR	18.42	0.65	0.02	0.63	3.7
AMR	19.43	0.71	0.18	0.53	25.2
EMR	20.32	1.04	0.12	0.92	11.2
EUR	18.97	0.68	0.26	0.42	37.9
SEAR	20.84	1.27	0.10	1.17	8.2
WPR	20.21	1.00	0.31	0.70	30.8
World	19.79	0.94	0.15	0.79	15.6
W Europe	18.60	0.55	0.24	0.31	43.7

Table 7.2. Total congenital malformations. Estimated potential and actual affected live birth prevalence and outcomes in 2010 by WHO region

WHO region	Potential (if no intervention) /1,000			% reduct-ion due to FAFF &/or TOP	Actual live births		Outcomes with current interventions			% reduction due to intervention		% effect-ive cure
	Live births	Under-5 deaths	Living @ 5 yr w disabil		Actual live births	% with access to care	Under-5 deaths	Living @ 5 yr w disabil	Effect-ive cure	in under-5 deaths	in disabil. at 5 yr	
AFR	17.8	7.9	8.4	0.5	17.7	3.9	6.5	8.5	0.7	17.7	-0.6	3.7
AMR	18.7	8.9	9.6	5.0	17.8	42.3	3.8	7.0	8.0	56.7	27.0	45.0
EMR	19.3	9.4	9.2	2.3	18.8	18.4	5.8	8.4	3.3	38.5	8.1	17.8
EUR	18.3	8.5	9.6	8.5	16.7	56.3	2.4	5.1	10.6	71.7	46.8	63.0
SEAR	19.6	9.6	9.2	1.5	19.3	10.4	6.3	9.3	2.1	34.3	-1.1	11.0
WPR	19.2	9.3	9.6	5.7	18.1	37.0	3.8	7.6	7.4	59.0	20.9	41.1
World	18.9	9.0	9.2	3.1	18.3	21.9	5.2	8.1	4.3	41.7	11.8	23.5
W Europe	18.0	8.3	9.7	9.3	16.4	69.0	1.5	4.1	12.9	82.2	57.3	78.9

7.1 Neural tube defects

This content is in preparation.

7.2 Oro-facial clefts

This content is in preparation.

7.3 Congenital heart disease

This content is in preparation.

7.4 Additional conditions

This content is in preparation.

Article 8: Congenital malformations: estimating outcomes of live births

Abstract

This article describes how available data on survival are used for creating life-time survival curves for different groups of congenital malformation, with optimal care and in the absence of care. The curves are then used to calculate the following by malformation group: (a) mean life expectancy; (b) years of life lost for the current birth cohort due to congenital malformation; (c) number and age distribution of survivors, living cured or with disability; (d) projected effects of future policy change on number and age distribution of survivors living cured or with disability.

Estimates for survival in the absence of care are based on reports from the older literature on survival before the introduction of current interventions, supplemented by expert opinion. Estimates of survival with optimal care are based on Tennant et al. (2010), adjusted for the effect of selective termination of more severely-affected pregnancies. In addition, in view of evidence of improved survival with congenital heart disease since 2000, mortality estimates are reduced by 20% for the years from 2000 onwards.

These survival curves are prospective, i.e. predict the future implications for affected individuals born in a given year. They are used to calculate mean life expectancy. This is then used (together with estimates for each malformation group of actual birth prevalence and proportion of correctable by paediatric surgery), to estimate total years of life affected, and years of life lost, or lived with disability or lived cured, per individual in the relevant birth cohort.

As an example of long-term outputs, Table 8.1 shows estimated years potentially and actually affected by congenital malformations per person in the 2010 birth cohort, together with estimated outcomes in terms of years of average years of life lost, lived with disability or cured per person in that birth cohort.

Table 8.1. Total congenital malformations: live births. Estimated potential and actual years affected, and outcomes per person born

WHO region	Potential if no intervention			% reduction in years affected due to FAFF &/or TOP	Actual years affected	Outcomes with current interventions			% reduction in		% Effect-ive cure
	Average years affected	Years of life lost	Years lived with disabil			Years of life lost	Years lived w disabil	Years lived cured	Years of life lost	Years lived w disabil	
AFR	1.02	0.69	0.33	0.0	1.01	0.63	0.35	0.04	8.7	-6.1	3.9
AMR	1.59	1.14	0.45	4.4	1.52	0.56	0.24	0.72	50.9	46.7	45.3
EMR	1.38	0.97	0.4	2.2	1.35	0.74	0.36	0.25	23.7	10.0	18.1
EUR	1.55	1.11	0.44	7.7	1.43	0.35	0.13	0.95	68.5	70.5	61.3
SEAR	1.37	0.97	0.4	1.5	1.35	0.81	0.39	0.15	16.5	2.5	10.9
WPR	1.49	1.05	0.44	5.4	1.41	0.55	0.27	0.59	47.6	38.6	39.6
World	1.35	0.94	0.4	3.0	1.31	0.65	0.34	0.32	30.9	15.0	23.7
W. Eur	1.69	1.21	0.48	7.7	1.55	0.23	0.04	1.27	81.0	91.7	75.1

The article also shows how the number and age distribution of living survivors is calculated for any given year, using population age distribution in the chosen year, and retrospective survival curves created taking account of services available at the time of birth of each 5-year age group.

Part III. Genetic disorders

Article 9: Haemoglobin disorders: a model for single gene disorders

Abstract

This content is in preparation.

Article 10: Single gene disorders

Abstract

This content is in preparation.

Article 11: Gene clustering and parental consanguinity

Abstract

This content is in preparation.

Article 12: Disorders due to genetic risk factors: rhesus haemolytic disease

Abstract

This content is in preparation.

Article 13: Disorders due to genetic risk factors: G6PD deficiency

Abstract

This content is in preparation.

Annexes

Annexes A: General Method

Annex A1: Comparison of GBD and Global Database under-5 mortality estimates

This content is in preparation.

Annex A2: Environmental disorders

This content is in preparation.

Annex A3: Different ways of expressing incidence

This content is in preparation.

Annex A4: Calculation of attributable early mortality

This content is in preparation.

Annex A5: Creating retrospective survival curves

This content is in preparation.

Annex A6: The need for better quantitative methods for assessing the burden of congenital disorders

This content is in preparation.

Annex A7: Assessing costs and benefits

This content is in preparation.

Annex A8: Evolution of infant mortality in Western Europe

This content is in preparation.

Annex A9: Bundling of countries /territories

This content is in preparation.

Annex A10: Comparison of estimates in March of Dimes 2006 report with Global Database estimates for 2010.

This content is in preparation.

Annexes B: Use of demographic data

Annex B1: Comparison of estimates from sequential WPP revisions

This content is in preparation.

Annex B2: Reason for limiting projections to 2050 (instead of 2100)

This content is in preparation.

Annex B3: Birth rate and infant mortality- the global development curve

This content is in preparation.

Annex B4: Charts illustrating use of sex ratios

This content is in preparation.

Annex B5: Relation between infant and under-5 mortality

This content is in preparation.

Annex B6: Effect of the HIV/AIDS epidemic in Southern Africa

This content is in preparation.

Annexes C: Calculating access to services

Annex C1: Correlation of potential indicators with IMR

This content is in preparation.

Annex C2: Adjustment of IMR for effects of parental consanguinity

This content is in preparation.

Annex C3: Adjustment of IMR for AIDS-related mortality

This content is in preparation.

Annex C4: Policies on prenatal diagnosis in 11 EUROCAT countries in 2005

This content is in preparation.

Annexes D: Chromosomal disorders

Annex D1: Clinical pictures

This content is in preparation.

Annex D2: Disability with chromosomal disorders

This content is in preparation.

Annex D3: Calculation of birth prevalence

This content is in preparation.

Annex D4: Adjustment for gestation at prenatal diagnosis

This content is in preparation.

Annex D5: Miscarriage, stillbirth and prematurity

This content is in preparation.

Annex D6: Rare chromosomal abnormalities

This content is in preparation.

Annex D7: Gestation at prenatal diagnosis (EUROCAT data)

This content is in preparation.

Annexes E: Congenital malformations 1 (birth prevalence)

Annex E1: Main groups of congenital anomalies

This content is in preparation.

Annex E2: "Other syndromes"

This content is in preparation.

Annex E3: Comparison of congenital malformation groups reported by EUROCAT and ICBDMR

This content is in preparation.

Annex E4: The problem of ascertainment

This content is in preparation.

Annex E5: Prematurity

This content is in preparation.

Annex E6: Age cut-off in EUROCAT registries (in 2010)

This content is in preparation.

Annex E7: Conversion of non-syndromic to isolated congenital malformations

This content is in preparation.

Annex E8: Fetal deaths

This content is in preparation.

Annex E9: Tables

This content is in preparation.

Annexes F: Congenital malformations 2 (survival)

Annex F1: Sources for survival data for congenital disorders

This content is in preparation.

Annex F2: Adjusting Tennant survival data for effect of termination of pregnancy

This content is in preparation.

Annex F3: Estimating survival with congenital malformations in the absence of diagnosis and care

This content is in preparation.

Annex F4: Estimating survival with untreated oro-facial cleft

This content is in preparation.

Annex F5: Calculating mean age at death

This content is in preparation.

Annex F6: Calculating years of life lost due to congenital disorders

This content is in preparation.

Annex F7: Grading disability

This content is in preparation.

Annex F8: Changes with time in interventions for live-born children with congenital disorders

This content is in preparation.

Table Annexe

For ease of use, the table annexe containing supplementary data is provided in machine readable format in the following files associated with this document online in UCL Discovery.

TA01-Bottom-Line-WHO-2017-04.xlsx

Contents:

- **Datasheet 1: Grand Total by WHO region**
  TOTAL constitutional congenital disorders /1,000 births, and av. annual numbers 2010-14, by WHO region and sub-region
- **Datasheet 2: Grand Total by country**
  TOTAL constitutional congenital disorders /1,000 births, and av. annual numbers 2010-14, by country, WHO sub-region and WHO region
- **Datasheet 3: Main group totals**
  Six groups of constitutional congenital disorders /1,000 births and av. annual numbers 2010-14, by country, WHO sub-region & region

TA02-Chromosomal-Disorders-WHO-2017-04.xlsx

Contents:

- **Grand Total by WHO region**
  TOTAL chromosomal disorders /1,000 births, and average annual numbers 2010-14, by WHO region and sub-region
- **Grand Total by country**
  3 groups of chromosomal disorders (Down syndrome, other autosomal, sex chromosomal) /1,000 births, and av. annual numbers 2010-14, by WHO region and sub-region
- **Main group totals**
  TOTAL chromosomal disorders /1,000 births and av. annual numbers 2010-14, by country, WHO sub-region & region

TA03-Congenital-Malformations-WHO-2017-04.xlsx

Contents:

- **WHO regions Grand Total**
  TOTAL congenital malformations /1,000 births, and av. annual numbers 2010-14, by WHO region and sub-region
- **WHO regions sub-groups**
  5 sub-groups of congenital malformations (NTDs, OFCs, CHD, other potentially lethal, other sub-lethal) /1,000 births, and av. annual numbers 2010-14, by WHO region and sub-region
- **Country Grand Total**
  TOTAL congenital malformations /1,000 births and av. annual numbers 2010-14, by country, WHO sub-region & region
- **Country sub-group rates**
  5 sub-groups of congenital malformations (NTDs, OFCs, CHD, other potentially lethal, other sub-lethal) /1,000 births, by country, WHO sub-region & region
- **Country sub-groups numbers**
  5 sub-groups of congenital malformations (NTDs, OFCs, CHD, other potentially lethal, other sub-lethal): average annual numbers, by country, WHO sub-region & region

- **Selected outputs April 2017**
  All the above estimates in one spreadsheet

TA04-Rare-single-gene-WHO-2017-04.xlsx

Contents:

- **WHO regions Grand Total**
  TOTAL rare single gene disorders /1,000 births, and average annual numbers 2010-14, by WHO region and sub-region
- **WHO regions Sub-groups**
  2 groups of rare single gene disorders (basic and consanguinity-associated) /1,000 births, and average annual numbers 2010-14, by WHO region and sub-region
- **Country Grand Total**
  TOTAL rare single gene disorders /1,000 births and average annual numbers 2010-14, by country, WHO sub-region & region
- **Country sub-group rates**
  2 groups of rare single gene disorders (basic and consanguinity-associated) /1,000 births, by country, WHO sub-region & region
- **Country sub-groups numbers**
  2 groups of rare single gene disorders (basic and consanguinity-associated): average annual numbers, by country, WHO sub-region & region
- **Selected outputs April 2017**
  All the above estimates in one spreadsheet

TA05-Hb-Disorders-WHO-2017-04.xlsx

Contents:

- **WHO regions Grand Total**
  TOTAL haemoglobin disorders /1,000 births, and av. annual numbers 2010-14, by WHO region and sub-region
- **WHO regions Sub-groups**
  3 groups of haemoglobin disorders (sickle cell disorders, beta thalassaemias, alpha thalassaemias) /1,000 births, and av. annual numbers 2010-14, by WHO region and sub-region
- **Country Grand Total**
  TOTAL haemoglobin disorders /1,000 births and av. annual numbers 2010-14, by country, WHO sub-region & region
- **Country sub-group rates**
  3 groups of haemoglobin disorders (sickle cell disorders, beta thalassaemias, alpha thalassaemias) /1,000 births, by country, WHO sub-region & region
- **Country sub-groups numbers**
  3 groups of haemoglobin disorders (sickle cell disorders, beta thalassaemias, alpha thalassaemias): average annual numbers, by country, WHO sub-region & region
- **Bundled outputs April 2017**
  All the above estimates in one spreadsheet
- **Detailed outputs, April 2017**
  6 groups of haemoglobin disorders classified clinically (Severe SCD, less severe SCD, Transfusion-dependent beta thalassaemia, less severe beta thalassaemia, lethal alpha thalassaemia, less severe alpha thalassaemia). This sheet also includes estimates of annual numbers of affected births, under-5 deaths and survivors at 5 yrs. with disability, with and without access to care.

TA06-Rhesus-WHO-2017-04.xlsx

Contents:

- **WHO regions Grand Total**
  Total Rhesus haemolytic disease: rate /1,000 births, and average annual numbers 2010-14, by WHO region and sub-region
- **Country rates per 1,000**
  Estimated Rhesus haemolytic disease /1,000 by country, WHO sub-region & region
- **Country annual numbers**
  Estimated annual Rhesus haemolytic disease by country, WHO sub-region & region, 2010-14
- **Selected outputs April 2017**
  Estimates downloaded, including all the above in one spreadsheet

TA07-G6PDd-NNJ-WHO-2017-04.xlsx

Contents:

- **WHO regions Grand Total**
  Total estimated G6PD deficiency neonatal jaundice: rate /1,000 births, and average annual numbers 2010-14, by WHO region and sub-region
- **Country rates per 1,000**
  Estimated G6PD deficiency neonatal jaundice /1,000 by country, WHO sub-region & region
- **Country annual numbers**
  Estimated annual G6PD deficiency neonatal jaundice by country, WHO sub-region & region, 2010-14
- **Selected outputs April 2017**
  Estimates downloaded, including all the above in one spreadsheet

TA08-Three-additional-conditions-WHO-2017-04.xlsx

Contents:

- **WHO regions Grand Total**
  TOTAL additional conditions /1,000 births, and average annual numbers 2010-14, by WHO region and sub-region
- **Diagnoses by WHO region**
  The three additional conditions /1,000 births, and average annual numbers 2010-14, by WHO region and sub-region
- **Country Grand Total**
  TOTAL additional conditions /1,000 births and average annual numbers 2010-14, by country, WHO sub-region & region
- **Country rates /1,000**
  Three additional conditions /1,000 births, by country, WHO sub-region & region
- **Country annual numbers**
  Three additional conditions: average annual numbers, by country, WHO sub-region & region
- **Selected outputs April 2017**
  All the above estimates in one spreadsheet

TA09-Comparison-with-GBD-WHO-2017-04.xlsx

Contents:

- **Comp GBD MGDb 2012 country**
  Global Database estimates of baseline birth prevalence of congenital ANOMALIES and outcomes in 2010: comparison of GBD and Global Database estimates of attributable under-5 mortality by country, WHO region and sub-region
- **Comp by WHO region**
  Global Database estimates of baseline birth prevalence of congenital ANOMALIES and outcomes in 2010: comparison of GBD and Global Database estimates of attributable under-5 mortality by WHO region and sub-region
- **Selected charts**
  Outputs and charts selected to enable assessment of the two sets of estimates

TA10-Months-Affected-WHO-2017-04.xlsx

Contents:

- **Method**
  Method by which these calculations are made
- **Total months life WHO region**
  Total constitutional congenital disorders: months affected /person born 2010-14, by WHO region and sub-region
- **Total months life country**
  Total constitutional congenital disorders: months affected /person born 2010-14, by country, WHO sub-region and WHO region
- **Months life by Main Groups**
  Total constitutional congenital disorders: months affected /person born for six groups of constitutional congenital disorders in 2010-14, by country, WHO sub-region & region

References

Alwan, A. d., B. Modell, A. Bittles, A. Czeizel and H. Hamamy (1997). Community control of genetic and congenital disorders, World Health Organisation. Office for the Eastern Mediterranean.

Ash, P., J. Vennart and C. O. Carter (1977). "The incidence of hereditary disease in man." Lancet **1**(8016): 849-851.

Baird, P. A. (1987). "Measuring birth defects and handicapping disorders in the population: the British Columbia Health Surveillance Registry." CMAJ **136**(2): 109-111.

Baird, P. A., T. W. Anderson, H. B. Newcombe and R. B. Lowry (1988). "Genetic disorders in children and young adults: a population study." Am J Hum Genet **42**(5): 677-693.

Baird, P. A. and A. D. Sadovnick (1987). "Life expectancy in Down syndrome." J Pediatr **110**(6): 849-854.

Baird, P. A. and A. D. Sadovnick (1988). "Life expectancy in Down syndrome adults." Lancet **2**(8624): 1354-1356.

Bhutani, V. K., A. Zipursky, H. Blencowe, R. Khanna, M. Sgro, F. Ebbesen, J. Bell, R. Mori, T. M. Slusher, N. Fahmy, V. K. Paul, L. Du, A. A. Okolo, M. F. de Almeida, B. O. Olusanya, P. Kumar, S. Cousens and J. E. Lawn (2013). "Neonatal hyperbilirubinemia and Rhesus disease of the newborn: incidence and impairment estimates for 2010 at regional and global levels." Pediatr Res **74 Suppl 1**: 86-100.

Bittles, A. H. and M. L. Black (2010a). "Evolution in health and medicine Sackler colloquium: Consanguinity, human evolution, and complex diseases." Proc Natl Acad Sci U S A **107 Suppl 1**: 1779-1786.

Bittles, A. H. and M. L. Black (2010b). "The impact of consanguinity on neonatal and infant health." Early Hum Dev **86**(11): 737-741.

Bittles, A. H. and J. V. Neel (1994). "The costs of human inbreeding and their implications for variations at the DNA level." Nat Genet **8**(2): 117-121.

Black, R. E., S. Cousens, H. L. Johnson, J. E. Lawn, I. Rudan, D. G. Bassani, P. Jha, H. Campbell, C. F. Walker, R. Cibulskis, T. Eisele, L. Liu, C. Mathers, W. H. O. Child Health Epidemiology Reference Group of, Unicef, R. E. Black, J. Bryce, L. Caulfield, C. F. Walker, H. Johnson, H. Kalter, J. Katz, L. Liu, N. Walker, D. Bassani, P. Jha, Z. Bhutta, T. Eisele, H. Campbell, I. Rudan, E. Theodoratou, S. Cousens, V. Filippi, M. Ezzati, C. Lanata, J. Lawn, H. Peterson, R. Steketee, R. Bahl, T. Boerma, T. Cherian, O. Fontaine, F. Gore, R. Hutubessy, J. Martines, L. Muhe, S. Qazi, D. Brown, M. Young, M. Chopra, M. Oestergaard, M. Inoue, D. M. Fat, V. Joseph, C. B. Pinto, N. Binkin, C. Weidemann, K. Chan, Y. Guo, R. Kumar, S. Awasthi, A. Adler, S. Oza, M. Aryee and L. Lamberti (2010). "Global, regional, and national causes of child mortality in 2008: a systematic analysis." Lancet (London, England) **375**(9730): 1969-1987.

Blencowe, H., T. Vos, A. C. Lee, R. Philips, R. Lozano, M. R. Alvarado, S. Cousens and J. E. Lawn (2013). "Estimates of neonatal morbidities and disabilities at regional and global levels for 2010: introduction, methods overview, and relevant findings from the Global Burden of Disease study." Pediatr Res **74 Suppl 1**: 4-16.

Bodmer, W. F. and L. L. Cavalli-Sforza (1976). Genetics, evolution, and man, WH Freeman San Francisco.

Bojesen, A., S. Juul, N. Birkebaek and C. H. Gravholt (2004). "Increased mortality in Klinefelter syndrome." J Clin Endocrinol Metab **89**(8): 3830-3834.

Bowman, R. M., D. G. McLone, J. A. Grant, T. Tomita and J. A. Ito (2001). "Spina bifida outcome: a 25-year prospective." Pediatr Neurosurg **34**(3): 114-120.

Bundey, S. and H. Alam (1993). "A five-year prospective study of the health of children in different ethnic groups, with particular reference to the effect of inbreeding." Eur J Hum Genet **1**(3): 206-219.

Campbell, M. (1968). "Natural history of persistent ductus arteriosus." Br Heart J **30**(1): 4-13.

Carter, C. O. (1958). "A Life-Table for Mongols with the Causes of Death." Journal of Mental Deficiency Research **2**(2): 64-74.

Carter, C. O. (1977). "Monogenic disorders." J Med Genet **14**(5): 316-320.

Christensen, K., K. Juel, A. M. Herskind and J. C. Murray (2004). "Long term follow up study of survival associated with cleft lip and palate at birth." BMJ **328**(7453): 1405.

Christianson, A., C. P. Howson and B. Modell (2006). "March of Dimes: global report on birth defects, the hidden toll of dying and disabled children." March of Dimes: global report on birth defects, the hidden toll of dying and disabled children.

Christianson, A. and B. Modell (2004). "Medical genetics in developing countries." Annu Rev Genomics Hum Genet **5**: 219-265.

Costa, T., C. R. Scriver and B. Childs (1985). "The effect of Mendelian disease on human health: a measurement." Am J Med Genet **21**(2): 231-242.

Cousens, S., H. Blencowe, C. Stanton, D. Chou, S. Ahmed, L. Steinhardt, A. A. Creanga, O. Tuncalp, Z. P. Balsara, S. Gupta, L. Say and J. E. Lawn (2011). "National, regional, and worldwide estimates of stillbirth rates in 2009 with trends since 1995: a systematic analysis." Lancet **377**(9774): 1319-1330.

Czeizel, A. and K. Sankaranarayanan (1984). "The load of genetic and partially genetic disorders in man. I. Congenital anomalies: estimates of detriment in terms of years of life lost and years of impaired life." Mutat Res **128**(1): 73-103.

Czeizel, A. E. (1997). "First 25 years of the Hungarian congenital abnormality registry." Teratology **55**(5): 299-305.

Elwood, J. M., J. Little and J. H. Elwood (1992). Epidemiology and control of neural tube defects, Oxford University Press.

EUROCAT (2009). Special Report: Congenital heart defects in Europe 2000-2005.

Fleming, A., J. Storey, L. Molineaux, E. Iroko and E. Attai (1979). "Abnormal haemoglobins in the Sudan savanna of Nigeria: I. Prevalence of haemoglobins and relationships between sickle cell trait, malaria and survival." Annals of Tropical Medicine & Parasitology **73**(2): 161-172.

Frid, C., P. Drott, P. Otterblad Olausson, C. Sundelin and G. Anneren (2004). "Maternal and neonatal factors and mortality in children with Down syndrome born in 1973-1980 and 1995-1998." Acta Paediatr **93**(1): 106-112.

Garne, E. (2013). Special Report: Coding of Congenital Heart Defects in the EUROCAT Database.

Gross, F. (1983). "Community Control of Hereditary Anemias - Memorandum from a WHO Meeting." Bulletin of the World Health Organization **61**(1): 63-80.

Harris, H. (1970). The principles of human biochemical genetics. Amsterdam, New York,, North-Holland Pub. Co.; American Elsevier Pub. Co.

Honein, M. A., R. S. Kirby, R. E. Meyer, J. Xing, N. I. Skerrette, N. Yuskiv, L. Marengo, J. R. Petrini, M. J. Davidoff, C. T. Mai, C. M. Druschel, S. Viner-Brown, L. E. Sever and N. National Birth Defects Prevention (2009). "The association between major birth defects and preterm birth." Matern Child Health J **13**(2): 164-175.

Hook, E. B. and J. Hamerton (1977). The frequency of chromosome abnormalities detected in consecutive newborn studies – differences between studies – results by sex and by severity of phenotypic involvement. . Population cytogenetics: studies in humans. E. B. Hook and I. H. Porter. New York, Academic Press.

Howes, R. E., F. B. Piel, A. P. Patil, O. A. Nyangiri, P. W. Gething, M. Dewi, M. M. Hogg, K. E. Battle, C. D. Padilla, J. K. Baird and S. I. Hay (2012). "G6PD deficiency prevalence and estimates of affected populations in malaria endemic countries: a geostatistical model-based map." PLoS Med **9**(11): e1001339.

Hunt, G. M. and P. Oakeshott (2003). "Outcome in people with open spina bifida at age 35: prospective community based cohort study." BMJ **326**(7403): 1365-1366.

Kadir, A., P. A. Mossey, H. Blencowe, S. Moorthie, J. E. Lawn, P. Mastroiacovo and B. Modell (2016). "Systematic Review and Meta-analysis of the Birth Prevalence of Orofacial Clefts in Low- and Middle-Income Countries." Cleft Palate Craniofac J.

Laurence, K. M. and B. J. Tew (1971). "Natural history of spina bifida cystica and cranium bifidum cysticum. Major central nervous system malformations in South Wales. IV." Arch Dis Child **46**(246): 127-138.

Lie, R. T., A. J. Wilcox and R. Skjaerven (2001). "Survival and reproduction among males with birth defects and risk of recurrence in their children." JAMA **285**(6): 755-760.

Liu, L., S. Cousens, J. E. Lawn and R. E. Black (2012). "Global regional and national causes of child mortality–Authors' reply." The Lancet **380**(9853): 1556-1557.

Liu, L., H. L. Johnson, S. Cousens, J. Perin, S. Scott, J. E. Lawn, I. Rudan, H. Campbell, R. Cibulskis, M. Li, C. Mathers, R. E. Black, W. H. O. Child Health Epidemiology Reference Group of and Unicef (2012). "Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000." Lancet **379**(9832): 2151-2161.

Lopez, A., C. Mathers, M. Ezzati, D. Jamison and C. Murray (2006). "Global Burden of Disease and Risk Factors: A copublication of Oxford University Press and The World Bank."

Lorber, J. (1971). "Results of treatment of myelomeningocele. An analysis of 524 unselected cases, with special reference to possible selection for treatment." Dev Med Child Neurol **13**(3): 279-303.

Lorber, J. and S. A. Salfield (1981). "Results of selective treatment of spina bifida cystica." Arch Dis Child **56**(11): 822-830.

Mason, J. K. and D. W. Meyers (1986). "Parental choice and selective non-treatment of deformed newborns: a view from mid-Atlantic." J Med Ethics **12**(2): 67-71.

Mathers, C. D. and D. Loncar (2006). "Projections of global mortality and burden of disease from 2002 to 2030." Plos med **3**(11): e442.

Modell, B. and V. Berdoukas (1984). "The clinical approach to thalassaemia." GRUNE AND STRATTON, NEW YORK, NY(USA). 1983.

Modell, B., R. J. Berry, C. A. Boyle, A. Christianson, M. Darlison, H. Dolk, C. P. Howson, P. Mastroiacovo, P. Mossey and J. Rankin (2012). "Global regional and national causes of child mortality." Lancet **380**(9853): 1556; author reply 1556-1557.

Modell, B. and M. Darlison (2008). "Global epidemiology of haemoglobin disorders and derived service indicators." Bull World Health Organ **86**(6): 480-487.

Modell, B., M. Khan and M. Darlison (2000). "Survival in beta-thalassaemia major in the UK: data from the UK Thalassaemia Register." Lancet **355**(9220): 2051-2052.

Modell, B., M. Khan, M. Darlison, M. A. Westwood, D. Ingram and D. J. Pennell (2008). "Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance." J Cardiovasc Magn Reson **10**: 42.

Modell, B., A. Kuliev and M. Wagner (1991). Community genetics services in Europe : report on a survey. Copenhagen, World Health Organization, Regional Office for Europe.

Modell, B. and M. Modell (1992). Towards a healthy baby : congenital disorders and the new genetics in primary care. Oxford ; New York, Oxford University Press.

Morris, J. K., E. Alberman, C. Scott and P. Jacobs (2008). "Is the prevalence of Klinefelter syndrome increasing?" Eur J Hum Genet **16**(2): 163-170.

Morris, J. K., D. E. Mutton and E. Alberman (2002). "Revised estimates of the maternal age specific live birth prevalence of Down's syndrome." J Med Screen **9**(1): 2-6.

Mossey, P. A. and J. Little (2002). Epidemiology of oral clefts: an international perspective. Cleft lip and palate : from origin to treatment. D. F. Wyszynski. Oxford, Oxford University Press**:** 127-158.

Mourant, A. E., A. C. Kopeć and K. Domaniewska-Sobczak (1976). The distribution of the human blood groups, and other polymorphisms. London, Oxford University Press.

Myrianthopoulos, N. C. and C. S. Chung (1974). "Congenital malformations in singletons: epidemiologic survey. Report from the Collaborative Perinatal project." Birth Defects Orig Artic Ser **10**(11): 1-58.

Nacul, L. C., A. Stewart, C. Alberg, S. Chowdhury, M. W. Darlison, C. Grollman, A. Hall, B. Modell, S. Moorthie, G. S. Sagoo and H. Burton (2014). "A Toolkit to assess health needs for congenital disorders in low- and middle-income countries: an instrument for public health action." J Public Health (Oxf) **36**(2): 243-250.

Neel, J. V. (1958). "A study of major congenital defects in Japanese infants." Am J Hum Genet **10**(4): 398-445.

Oakeshott, P. and G. M. Hunt (2003). "Long-term outcome in open spina bifida." Br J Gen Pract **53**(493): 632-636.

Pedersen, R. N., E. Garne, M. Loane, L. Korsholm, S. Husby and E. W. Group (2008). "Infantile hypertrophic pyloric stenosis: a comparative study of incidence and other epidemiological characteristics in seven European regions." J Matern Fetal Neonatal Med **21**(9): 599-604.

Penrose, L. S. (1949). "The incidence of mongolism in the general population." J Ment Sci **95**(400): 685-688.

Platt, O. S., D. J. Brambilla, W. F. Rosse, P. F. Milner, O. Castro, M. H. Steinberg and P. P. Klug (1994). "Mortality in sickle cell disease. Life expectancy and risk factors for early death." N Engl J Med **330**(23): 1639-1644.

Price, W. H., J. F. Clayton, S. Collyer, R. De Mey and J. Wilson (1986). "Mortality ratios, life expectancy, and causes of death in patients with Turner's syndrome." J Epidemiol Community Health **40**(2): 97-102.

Raju, S. (2000). "In search of a smile: Study of children born with cleft lips and palates in India." Mumbai, Tata Institute of Social Sciences.

Skjaerven, R., A. J. Wilcox and R. T. Lie (1999). "A population-based study of survival and childbearing among female subjects with birth defects and the risk of recurrence in their children." N Engl J Med **340**(14): 1057-1062.

Stanton, C., J. E. Lawn, H. Rahman, K. Wilczynska-Ketende and K. Hill (2006). "Stillbirth rates: delivering estimates in 190 countries." Lancet **367**(9521): 1487-1494.

Stevenson, A. C. (1959). "The load of hereditary defects in human populations." Radiation research supplement **1**: 306-325.

Stevenson, A. C., H. A. Johnston, M. I. Stewart and D. R. Golding (1966). "Congenital malformations. A report of a study of series of consecutive births in 24 centres." Bull World Health Organ **34 Suppl**: 9-127.

Stochholm, K., S. Juul, K. Juel, R. W. Naeraa and C. H. Gravholt (2006). "Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome." J Clin Endocrinol Metab **91**(10): 3897-3902.

Tennant, P. W., M. S. Pearce, M. Bythell and J. Rankin (2010). "20-year survival of children born with congenital anomalies: a population-based study." Lancet **375**(9715): 649-656.

Trimble, B. K. and J. H. Doughty (1974). "The amount of hereditary disease in human populations." Ann Hum Genet **38**(2): 199-223.

United Nations. Scientific Committee on the Effects of Atomic Radiation. (1977). Sources and effects of ionizing radiation : 1977 report to the General Assembly, with annexes. New York, United Nations.

United Nations. Scientific Committee on the Effects of Atomic Radiation. and United Nations. General Assembly. (1982). Ionizing radiation : sources and biological effects : 1982 report to the General Assembly, with annexes. New York, United Nations.

United Nations. Scientific Committee on the Effects of Atomic Radiation. and United Nations. General Assembly. (1986). Genetic and somatic effects of ionizing radiation : United Nations Scientific Committee on the Effects of Atomic Radiation : 1986 report to the General Assembly, with annexes. New York, United Nations.

Visootsak, J. and J. M. Graham, Jr. (2006). "Klinefelter syndrome and other sex chromosomal aneuploidies." Orphanet J Rare Dis **1**: 42.

Wellesley, D., H. Dolk, P. A. Boyd, R. Greenlees, M. Haeusler, V. Nelen, E. Garne, B. Khoshnood, B. Doray, A. Rissmann, C. Mullaney, E. Calzolari, M. Bakker, J. Salvador, M. C. Addor, E. Draper, J. Rankin and D. Tucker (2012). "Rare chromosome abnormalities, prevalence and prenatal diagnosis rates from population-based congenital anomaly registers in Europe." Eur J Hum Genet **20**(5): 521-526.

WHO (1985a). Community approaches to the control of hereditary diseases. Report of a WHO Advisory Group on Hereditary Diseases. Geneva 3‑5 October 1985. Unpublished WHO document.

WHO (1985b). Glucose-6-Phosphate Dehydrogenase Deficiency. Report of a WHO Working Group.

WHO (2000). Primary health care approaches for prevention and control of congenital and genetic disorders : report of a WHO meeting, Cairo, Egypt, 6-8 December 1999. Geneva, World Health Organization**:** 43 p. + annexes.

WHO (2006). Neonatal and perinatal mortality : country, regional and global estimates. Geneva, World Health Organization.

WHO and March of Dimes (2006). Management of birth defects and haemoglobin disorders : report of a joint WHO-March of Dimes meeting, Geneva, Switzerland, 17-19 May 2006. Geneva, World Health Organization**:** 27 p.

World Health Organization. (2004). International statistical classification of diseases and related health problems. Geneva, World Health Organization.

Wren, C., C. A. Irving, J. A. Griffiths, J. J. O'Sullivan, M. P. Chaudhari, S. R. Haynes, J. H. Smith, J. R. Hamilton and A. Hasan (2012). "Mortality in infants with cardiovascular malformations." Eur J Pediatr **171**(2): 281-287.

Wren, C. and J. J. O'Sullivan (2001). "Survival with congenital heart disease and need for follow up in adult life." Heart **85**(4): 438-443.

Wu, J., A. Springett and J. K. Morris (2013). "Survival of trisomy 18 (Edwards syndrome) and trisomy 13 (Patau Syndrome) in England and Wales: 2004-2011." Am J Med Genet A **161A**(10): 2512-2518.