Title

Congenital disorders: Epidemiological methods for answering calls for action

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Introduction

The importance of congenital disorders (also called *birth defects*) as a cause of early death and disability becomes increasingly apparent as countries pass through the development window and background mortality falls (Malherbe et al. 2015). Consequently there is growing recognition of the need for their care and prevention, particularly in low and middle-income countries. In 2010 the World Health Assembly (WHA) expressed concern that birth defects are still not recognized as a priority in public health, and called upon its member states to strengthen the prevention of congenital disorders and provision of care for those affected (World Health Assembly 2010). Nevertheless the 2015 International Conference on Birth Defects and Disabilities in the Developing World concluded that "as the Sustainable Development Goals are adopted by United Nations member states, children with congenital disorders remain left behind in policies, programs, research, and funding" (Darmstadt et al. 2016).

In fact two WHO regional offices (those for the Eastern Mediterranean and South-East Asia) have responded to the call from World Health Assembly. In the process, both have encountered important barriers to the development of health policy in this area. Firstly, policy requires a sound epidemiological base, but in most middle and low-income countries the combination of (a) limited resources for the correct and accurate diagnosis of congenital disorders and (b) inadequate information systems leads to gross under-estimation of the contribution of congenital disorders to early death and disability (Christianson et al. 2006; Christianson and Modell 2004; World Health Organization 1999). Secondly, the extreme diversity of congenital disorders makes them difficult to grasp collectively at a strategic public health level. Thirdly, these problems are compounded by failure to agree and implement precise and rigorous technical terminology (World Health Organization 2006). The database described in the following articles - the Modell Global Database of Congenital Disorders (MGDb) - has been developed in order to overcome these barriers to service development.

Congenital disorders

The World Health Organization defined congenital disorders as "any potential pathological conditions arising before birth, whether evident at birth or manifesting later in life (World Health Organization 2000; World Health Organization 2005; World Health Organization 2006). Using this definition congenital disorders fall into two main groups: *environmental congenital disorders* due to maternal exposure to infection, malnutrition or harmful environmental agents (Wittenburg 2009), and *congenital disorders with principally endogenous causes*. This second group, here collectively called *constitutional congenital disorders*, includes chromosomal disorders, the majority of congenital malformations, single gene disorders, and disorders due to genetic risk factors.

In 2006 the March of Dimes published provisional estimates of the global birth prevalence of congenital disorders (Christianson et al. 2006). The report was endorsed by the World Health Organization (World Health Organization 2006) and led to the World Health Assembly Resolution on Birth Defects (World Health Assembly 2010). This noted the lack of sound estimates of the number of children born with a serious congenital disorder, and

recommended (a) collection of data on the global burden of mortality and morbidity due to birth defects and (b) resolution of divergent opinions on their health burden.

While the specialist literature contains a wealth of high quality information on prevalence and outcomes of congenital disorders, neither the data nor its collective implications have been effectively communicated to the global or national public health communities. In addition, though the experience in high income countries shows that around 70% of congenital disorders can be prevented or successfully treated (Alwan and Modell 2003; Czeizel et al. 1993; World Health Organization 1996), this requires a range of interventions – treatments and preventive measures– that were introduced piecemeal as they evolved, but which have never been recognised as forming a single coherent package of care. The MGDb aims to overcome these difficulties by harnessing whatever data there is to generate evidence-based epidemiological estimates for congenital disorders. Recognising that public health policy-makers and primary care services prefer to deal with packages of care appropriate for delivery at different life stages rather than with single issues, it is helpful to group interventions with known effects into a portfolio of options that policy-makers can consider for integration into compartments of health services.

The primary focus of past international policy recommendations has been on preventing environmental congenital disorders, because public health initiatives including immunisation, micronutrient supplementation, avoidance of harmful exposures and appropriate pregnancy care, can reduce their prevalence by 90% or more. We estimate that as a result their global birth prevalence has fallen by approximately 50% so that they now make up around 15% of total congenital disorders. In contrast, the far larger group of constitutional disorders has been relatively neglected in public health policy-making, though their importance emerges as other causes of early mortality and disability are brought under control and countries transition epidemiologically. The main challenge that remains is that of developing effective policies for prevention and care of this large and diverse disorder group.

Assembling a global epidemiological evidence base

In response, an international expert group came together to identify, assemble, interpret and triangulate epidemiological information from a wide range of sources and to relate it to global demographic data in order to estimate the birth prevalences and outcomes of constitutional congenital disorders at the country, WHO region and global levels, and express the results in the scientific language of public health. Products of this process included the prototype MGDb implementation and the associated methods (the focus of this special issue), and the publication online of the first selected country-specific data (Table Annexes published as part of Modell et al. 2016) with related resources collected on a dedicated website[1].

The aims of the MGDb are (a) to provide order-of magnitude estimates for every country, which can be used to support policy-making when available observational data is inadequate, and (b) to encourage local public health officials, policy makers, their expert advisors, and non-governmental advocates to participate by generating their own estimates for comparison with available local observational data. Accordingly, the database was developed with the following guiding principles.

[1] http://mgdb.info

- The methods used must be as simple and reproducible as possible.
- It should use collective data sources that are as robust and as authoritative as possible, ideally freely available online – i.e. it should build on comprehensive datasets assembled and routinely published by others[2].
- Methods must be shared in full detail (Modell et al. 2016).
- Despite their variety, congenital disorders must be aggregated into manageable groups, and outcomes must be described in terms relevant to public health, such as effect of interventions on early mortality, disability and service need.
- All estimates must be made for every country, even (especially) when no observational data are available. In such cases an estimate must be used that is as evidence-based as reasonably possible.[3]
- Since estimates are offered for use in policy development, the priority is to avoid over-estimation. All estimates should be the lowest compatible with available data.

Current MGDb estimates indicate that at present, worldwide, annually, over 5 million births are affected with a congenital disorder, resulting in over 400 000 fetal deaths, 2.5 million under-5 deaths and 2 million survivors with significant disability at 5 years[4]. Hitherto the primary emphasis in reviewing adverse outcomes of congenital disorders has been on reducing mortality. The prevention of and care for the disability that results requires at least equivalent attention, since with increasing access to more effective care comes a steady rise in numbers surviving with disability and a greater need for disability services worldwide.

MGDb estimates also confirm that full deployment of available interventions could both reduce the birth prevalence of *environmental* congenital disorders to a very low level, *and* reduce adverse outcomes of *constitutional* congenital disorders by 50-80%.

The need for agreed terminology

Ostensibly, there are wide differences between current estimates of mortality and disability due to congenital disorders produced by the Global Burden of Disease study (GBD) and WHO on the one hand, and the March of Dimes and MGDb on the other (Liu et al. 2012a; Liu et al. 2012b; Lozano et al. 2012; Modell et al. 2012). However a considerable part of the difference reflects a lack of agreed technical terminology for reporting. For example GBD makes estimates for *congenital anomalies* as defined in Chapter XVII ("the Q chapter") of the International Classification of Diseases: "congenital malformations, deformations and chromosomal abnormalities" (Vos et al. 2017; World Health Organization 1992), but this covers only the sub-set of congenital disorders associated with *anatomical* abnormality. However, the term *congenital anomalies* is often used loosely to represent *all* congenital

[2] Examples include: United Nations World Population Prospects (WPP) demographic data, EUROCAT and ICBDSR umbrella congenital anomaly registries, Livingstone's database of haemoglobin disorders and G6PD deficiency (Livingstone 1985), Murdock's ethnographic atlas (Murdock 1967), Bittles' consanguinity database at consang.net, Institute for Health Metrics and Evaluation (IHME) global burden of disease (GBD) study outputs, and key published articles e.g. Tennant et al. mortality estimates (2010).
[3] Note the great nuclear physicist Fermi's famous recommendations: not to devote more time and effort to a problem than it is worth, and not to make something more accurate than absolutely necessary.
[4] Global estimates for 2010-14: actual affected birth prevalence = 37.4/1,000, leading to 3/1,000 fetal deaths, 17.9/1,000 under-5 deaths and 15/1,000 survivors with disability at 5 years.

disorders, and as a result the GBD estimates are easily misinterpreted, with the profound consequence that the burden of congenital disorders is grossly under-estimated. For this reason the first recommendation of the 2015 International Conference on Birth Defects and Disabilities in the Developing World was "to build consensus on a standardized definition of congenital disorders and promote its widespread use" (Darmstadt et al. 2016). The proposed definition – "abnormalities of structure or function which are present from birth" – corresponds closely with the WHO definition used in the MGDb (World Health Organization 2006).

In the course of building the database we encountered many other examples showing the need for technical scientific consensus on the terminology for congenital disorders: in order to proceed we created and shared a set of provisional working definitions for consultation (Modell et al. 2016).

WHO regional initiatives

The WHO Eastern Mediterranean Region (EMR) has a particularly high prevalence of congenital disorders, partly related to the local high prevalence of parental consanguinity (Alwan et al. 1997). Many of the disorders that are commonly diagnosed in the region are preventable using low cost, high impact interventions such as food fortification and immunisation. Paediatric surgery has been recognized as a priority intervention for preventing newborn and infant deaths due to congenital malformations and gaining years of life cured or without disability. Screening for genetic reproductive risk, genetic counselling and prenatal diagnosis with the option of termination of pregnancy, implemented in some countries of the region, has significantly reduced the birth prevalence of thalassaemia and may affect other single gene disorders similarly in the future. Meanwhile it has become clear that interventions that reduce mortality due to congenital disorders lead to a cumulative increase in numbers surviving with life-long disability and needing access to appropriate health services. However these interventions are not available to all families in the region. Some are costly, and many couples may not be aware of their existence. Hence, universal coverage is one of the main challenges for services aiming to reduce the burden of congenital disorders for families and the population as a whole. Responding to this situation, the WHO Regional Office for the Eastern Mediterranean (EMRO) has (a) supported the development of the MGDb in order to obtain independently-generated benchmark epidemiological estimates for EMR countries and (b) embarked on a maternal and child health-led programme aiming to strengthen pre-conception care through high impact, cost-effective and evidence-based interventions, and to support the efforts of Member States to address the burden of congenital disorders (World Health Organization 2015).

Similarly, the WHO Regional Office for South-East Asia (SEARO) is actively developing and implementing a regional strategic framework for prevention and control of birth defects (World Health Organization 2013).

Wider use of the methods

This special issue shows that the methods used in the MGDb to generate estimates of the birth prevalence and outcomes of congenital disorders are simple and reliable enough to be used within any Ministry of Health, as well as by groups advocating appropriate service development. An important limitation is that MGDb estimates apply only for whole

countries: this is often inadequate, particularly for large, diverse countries such as Brazil, China, India, or South Africa. Application of MGDb methods to generate within-country estimates has been piloted in South Africa, resulting in a local epidemiological database, the MGDb-ZA, which applies the methods to locally-sourced demographic data to generate estimates of the burden of congenital disorders at sub-national civil divisions (provinces in South Africa). Typically for a middle-income country, South Africa lacks empirical data for congenital disorders (Lebese et al. 2016): the MGDb-ZA now offers a tool to leverage increased political commitment to prioritise congenital disorders as a health care issue and develop the necessary services for care and prevention (Malherbe et al. 2015). A significant part of the work in establishing MDGb-ZA lay in identifying the most relevant and robust data sources in-country, a process that in itself led to the development of key partnerships and collaborations, and attracted the interest of policy-makers even before the initial estimates were available.

Content of this special issue

The first, historical article in this series shows that efforts to understand the global burden of congenital disorders have been underway for many years, and describes the step-wise evolution of the MGDb, starting from a WHO request for epidemiological information on haemoglobin disorders and progressing gradually towards comprehensive coverage of severe, early-onset congenital disorders.

The second article summarises the general approach used, reviews its strengths and limitations, and presents selected outputs by WHO region and globally. In particular it shows that the baseline birth prevalence (in the absence of any intervention) of constitutional congenital disorders is relatively constant in any given population, and the only possible outcomes are fetal death, early mortality, disability or cure. This unique characteristic confers exceptional advantages from an epidemiological point of view, because baseline birth prevalence both provides a solid starting point for quantitative assessment of the effects of interventions, and constitutes an envelope that must be filled by the sum of outcomes. That is, these disorder groups can be handled as closed systems.

The third article describes key interventions that are incorporated into the MGDb. Importantly, it also describes the derivation of an equation based on infant mortality rate that can be used to estimate the proportion of a population with access to these interventions, and so to estimate the potential and actual current effects of their deployment on early mortality and disability.

Subsequent articles describe methods that can be used to estimate the prevalence and outcomes of the main groups of constitutional congenital disorders plus summaries of the history, aims and current status of the two “umbrella” congenital anomaly registries – ICBDSR and EUROCAT – that provide the basis for global estimates for congenital malformations and chromosomal disorders. More detailed descriptions of MGDb methods and additional articles on haemoglobin disorders, rhesus negativity and G6PD deficiency are available online (Modell et al. 2016).

Conclusion

The articles in this special issue show that the MGDb estimates of the birth prevalence and outcomes of congenital disorders have a strong evidence base, and should be taken into consideration by health policy-makers world-wide.

At the international level they should encourage authorities including the WHO and the Global Burden of Disease study to raise congenital disorders in the ranking of global health priorities. At the country level they can contribute to the appropriate development of programmes for prevention and care of congenital disorders. For example, the WHO Regional Office for South East Asia recommends that each Ministry of Health designate a national focal point within the ministry and establish a national technical working group to develop a national strategic plan for prevention and control of congenital disorders (World Health Organization 2013). The MGDb estimates contribute significantly to the obvious first task of such a national working group, namely to review available data on the local causes, birth prevalence and outcomes of congenital disorders, and assess appropriate available interventions, their costs and their benefits.

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