Check for updates

Received: 28 January 2020 | Revised: 30 January 2020 | Accepted: 30 January 2020

DOI: 10.1002/ajmg.c.31775

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART C Seminars in Medical Genetics WILEY

From cause to care: Can a triple approach to better population data improve the global outlook of congenital heart disease?

Lorenzo D. Botto

Division of Medical Genetics, Department of Pediatrics, University of Utah, Salt Lake City, Utah

Correspondence
Lorenzo D. Botto, Division of Medical Genetics, Department of Pediatrics, University of Utah, 295 Chipeta Way, Salt Lake City, Utah 84108
Email: lorenzo.botto@hsc.utah.edu

Abstract

Congenital heart disease (CHD) is common, costly, and critical. Approximately half of all infant deaths due to congenital anomalies are associated with CHD or neural tube defects. As infant mortality improves due to better infection control and peripartum care, congenital anomalies are becoming a key driver of pediatric survival and health. Improving CHD prevention and care globally will play a significant role toward key goals such as United Nation's sustainable development goals (SDGs) of good health and well-being (SDG 3) and reduced inequalities (SDG 10). This review addresses two questions: how can we reinterpret and reframe available data on CHD to spur action in prevention and care? How can we re-engineer how we currently track CHD in populations to efficiently generate new *data* to assess successes and detect gaps in prevention and care? Answering these questions requires understanding the causal chain of disease, from cause to CHD occurrence to health outcomes. This perspective provides a logical basis for two innovations. First, develop a data-driven message that reframes epidemiologic and clinical data in terms of incentives for action, evidence for change, and strategies for population-wide impact. Second, through partnerships between clinical and public health systems, implement an integrated "triple surveillance," which, in the same population, concurrently tracks the three elements of the causal chain—causes, disease occurrence, health outcomes. By streamlining activities and minimizing operational waste, such systems can have a vital role in improving prevention and care on a population level, including in many low and middle-income countries.

KEYWORDS

congenital heart disease, genetics, prevention, public health, surveillance

1 | INTRODUCTION: DATA ARE FOR ACTION

Congenital heart disease (CHD) is common, costly, and critical. Approximately half of all infant deaths due to congenital anomalies are associated with CHD or neural tube defects (Christianson, Howson, & Modell, 2006). As infant mortality improves due to better infection control and peripartum care, congenital anomalies are increasingly becoming key drivers of pediatric survival and health (Christianson et al., 2006), a finding recently underscored by a report from the Global Burden of Disease 2017 (G. B. D. Congenital Heart Disease Collaborators, 2020), In many countries already, and even more in the future, improving CHD prevention and care globally will play a significant role toward key health goals such as the United Nation's sustainable development goals (SDGs) of good health and well-being (SDG 3) and reduced inequalities (SDG 10) (World Health Organization, 2020).

Global action depends on many factors, including a nation's priorities, its resources, its infrastructure, and its culture. However, a common foundation for effective action is knowledge of the challenge—the ability to understand and reliably track the reality of what is happening locally on the ground. Only by understanding the current state, one can build a realistic and practical path toward the ideal state—one with

 © 2020 Wiley Periodicals, Inc.

better health, better quality of life, and greater equity. Data generates information, and information that is appropriately filtered and interpreted generates knowledge. Knowledge can then be used for action. Such foundational knowledge of the population impact of CHD is scarce everywhere, especially in low resources areas of the world, but also in high-income countries. For example, many wealthy countries lack reliable and timely information on the prevalence and health impact of CHD beyond infancy and childhood.

This review provides a personal view on two key questions: can we approach and reinterpret *available data* on CHD to spur action in prevention and care? How can we re-engineer the way we currently track CHD in populations to efficiently generate *new data* that tracks successes and gaps in prevention and care? This view reflects an "activist" approach to clinical and epidemiologic data, one that views observation and reporting not in isolation but as a driving force for action and change. This approach to both questions starts with appreciating and embracing the causal chain that leads to the population impact of CHD.

2 | UNDERSTANDING THE CAUSAL CHAIN

In its simplest form, the causal chain has three measurable components—causes, disease occurrence, and health outcomes (Figure 1).

The degree to which a community is exposed to CHD risk factors (e.g., diabetes, smoking, advanced maternal age, consanguinity) represents the "burden of risk" of that population. Primary prevention acts by reducing such burden of risk. Disease occurrence (e.g., the prevalence of CHD at birth and throughout life) creates the conditions for adverse health outcomes. Together, CHD occurrence and health outcomes represent a population's "burden of disease."

Clearly, decreasing the burden of disease depends both on primary prevention (which decreases disease occurrence) and on care (which improves outcomes among people born with CHD). Though this framework may appear simplistic, it provides a logical basis for addressing the two key questions posed above—reinterpreting and generating data for action.

3 | REINTERPRETING CHD KNOWLEDGE FOR ACTION: INCENTIVES, EVIDENCE, AND STRATEGIES

One approach to reframing data for action reinterprets the information in the causal chain in terms of incentives, evidence, and strategies (Botto, 2015) (Figure 2).

Data on the health impact of CHD is now recast as *the cost of inaction* or the benefits of action—either way—the **incentive to act**. What to do is based on **evidence**—knowledge of modifiable factors that can prevent CHD and improve health outcomes. When such robust evidence is in hand, the issue to solve becomes one of **strategies:** how to translate the evidence into effective interventions that improve outcomes and reduce disparities across the population.

These three elements are more fully discussed elsewhere (Botto, 2015) and are briefly illustrated in the section below. Primary data are summarized in several reviews (Botto, 2013; Jenkins et al., 2007; Riehle-Colarusso & Patel, 2014).

3.1 | Incentive

A clear incentive for action is the burden of disease in the community—the combined second and third elements of the causal chain (Figure 1). Good data—reliable and timely—on the burden of disease provides a stark and powerful message to both community and policy makers. In addition, such data will also highlight local gaps in data and help realize just how much of the disease burden of CHD is still invisible.

For example, a reasonable estimate of the birth prevalence of major CHD is ~1% (Figure 3), with some variation across studies that depend mostly on whether milder conditions such as bicuspid aortic valve and patent ductus arteriosus are included. Severe CHD, which account for most of the disease burden in the population, affect ~1 in 400 newborns (2.5 per 1,000). This figure is much more consistent across high quality studies (Figure 3). Examples of severe CHD include single ventricle, heterotaxy, conotruncal defects, atrioventricular septal defects, total anomalous venous return, hypoplastic left heart, coarctation of the aorta, interrupted aortic arch, and pulmonary atresia.

These same figures are perhaps more compelling when viewed across populations worldwide (Figure 4). At this scale, two points deserve special emphasis. First, an estimated 1.2 million babies with CHD are born every year (9 per 1,000 of 135 million births). At least 300,000 (2–3 per 1,000) will have severe CHD conditions that require immediate specialized care for survival.

Second, most affected babies will be born in countries with few of the resources needed for optimal treatment and management (Figure 5).

The same expert group from the global burden of disease study estimated that in "low socio-demographic index" countries, between 1990 and 2017 CHD moved from being the 13th leading cause of

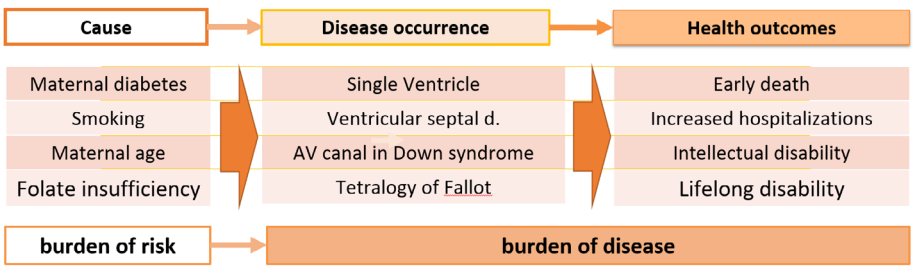

FIGURE 1 Simplified causal chain from causes of congenital heart disease to health outcomes. AV, atrioventricular

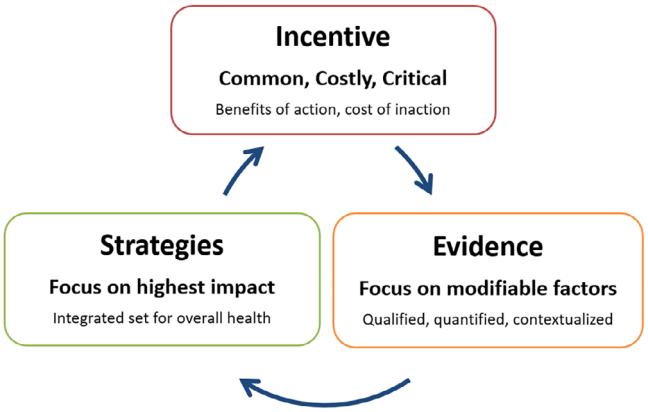

FIGURE 2 The cycle from epidemiology to prevention: incentive, evidence, strategies

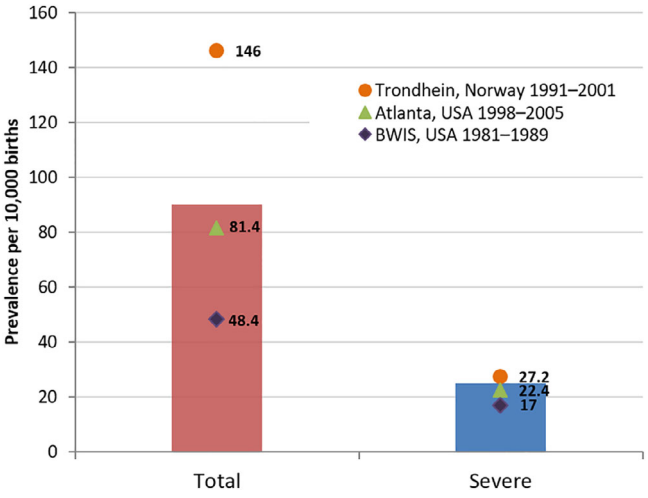

FIGURE 3 Birth prevalence of major congenital heart defects (overall and severe) in three studies, from (Botto, 2015). Bars represent approximate averages from the literature (overall rate, 9 per 1,000; rate for severe heart defects, 2.5 per 1,000)

death in children younger than 1 year to the eighth leading cause (G. B. D. Congenital Heart Disease Collaborators, 2020).

Clearly, all countries have significant incentives for improving CHD care and prevention. However, it is arguably in those large areas of the world where specialized resources for care are particularly scarce that primary prevention represents an especially transformative opportunity to decrease the overall CHD-related burden of disease.

Notably, such a survey of available data also highlights the major existing gaps in data. In fact, in many low and middle-income countries even basic metric of burden of disease such as CHD prevalence at birth or in infancy are not available except perhaps from small areas or through estimates (rather than directly derived from local data). Even less is known about CHD prevalence and impact beyond infancy and childhood, an increasingly important issue for population health, as more children survive to become adolescents and adults. Such data scarcity is a global challenge. Even in high income countries such figures tend to be based on modeling (Warnes et al., 2001) or on linkages between administrative databases (Marelli, Mackie, Ionescu-Ittu, Rahme, & Pilote, 2007). In North America, for example, it has been estimated that nearly 1 in every 200 people (all ages) is living with a CHD, and now adults have surpassed children (Marelli et al., 2007; Warnes et al., 2001). The most recent report of the Global Burden of Disease 2017 estimated that 12 million people are living with CHD globally, resulting in approximately 600,000 years lived with disability (G. B. D. Congenital Heart Disease Collaborators, 2020). The authors of the report are careful in pointing the limitations of these estimates, including the near complete lack of direct data from many countries, the potential for underreporting within available data, the inability of the type of coded data to represent the full spectrum of CHD, and the necessity to use cross-sectional data to infer longitudinal trends (G. B. D. Congenital Heart Disease Collaborators, 2020). Nevertheless, this landmark study provides a thoughtful and explicit set of global estimates, highlights significant gaps in knowledge, and underscores the massive health disparities currently occurring—all of which are critically important in raising awareness (the "incentive" for change) and providing a baseline for strategic interventions.

Another point deserving emphasis as an incentive for policymakers is the degree to which CHD affects the wealth of nations. In the United States, CHD overall includes the most expensive of all congenital anomalies (Keren and others, 2012; Robbins et al., 2007) and in children's hospitals CHD are regularly in the top tier of cost (Keren and others, 2012). For example, the cost of one year of CHD hospitalizations in 2004 was 1.4 billion US dollars (Botto, 2013; Boulet, Grosse, Riehle-Colarusso, & Correa-Villasenor, 2010; Centers for Disease Control and Prevention and others, 1995; Waitzman, Romano, & Scheffler, 1996). Lifetime costs, a more accurate estimate of the benefits of better prevention and care, have been extremely difficult to generate. A nearly 30 year-old study estimated lifetime costs of 1.2 billion (in 1992 dollars) for a single year birth cohort for children with one of four types of CHD—truncus arteriosus, d-transposition of the great arteries, tetralogy of Fallot, single ventricle (Centers for Disease Control and Prevention and others, 1995; Waitzman et al., 1996). Indirect costs such as loss of productivity, which not represented in most cost studies, were a significant fraction of total costs in this study, underscoring how most economic analyses likely represent underestimates of the true societal costs of CHD.

The impact of mortality and morbidity on populations is only slightly better known. Globally, because of their frequency and severity, CHD is the leading cause of *infant* deaths due to congenital anomalies—accounting for 1 in 3 such infant deaths (Lopez & Mathers, 2006; Rosano, Botto, Botting, & Mastroiacovo, 2000). In developed countries, congenital heart defects are estimated to account for ~1 in 10 infant deaths from *any* cause (Lopez & Mathers, 2006; Rosano et al., 2000). The contribution of CHD to *neonatal* deaths is also significant—in the United States (, 2010) and in several European countries (Dolk, Loane, & Garne, 2011), CHD accounts for an estimated 1 in 4 neonatal deaths due to congenital anomalies.

More globally, using sophisticated modeling approaches, an expert group from the Global Burden of Disease 2017 study estimated that

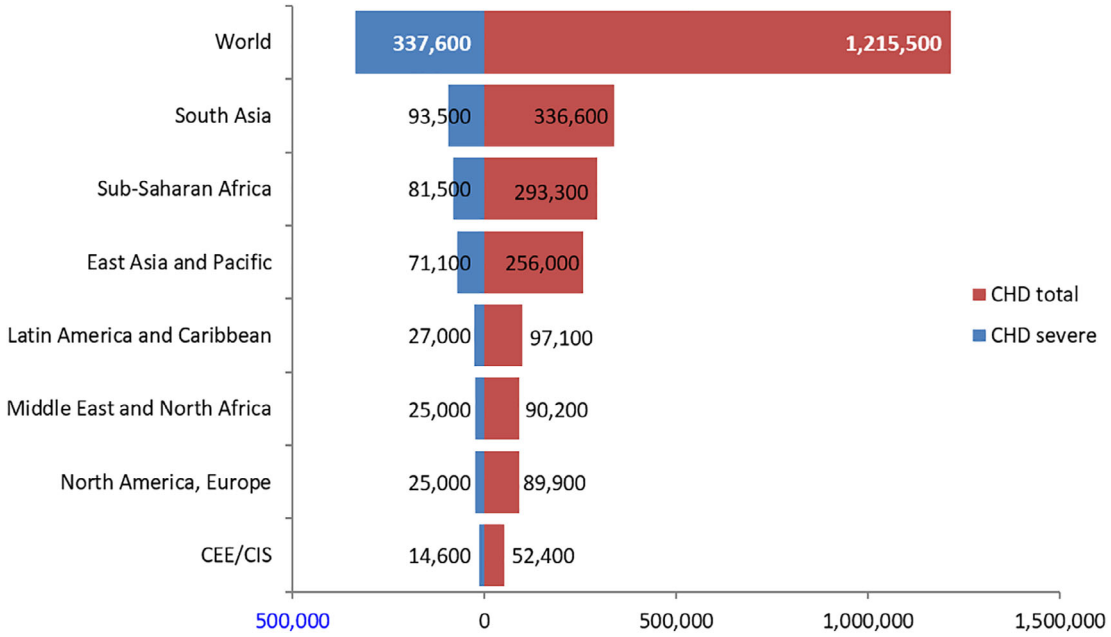

FIGURE 4 Estimated number of babies born yearly in different regions of the world with major heart defects (birth prevalence, 9 per 1,000) and with severe heart defects (2.5 per 1,000) from Botto (2015)

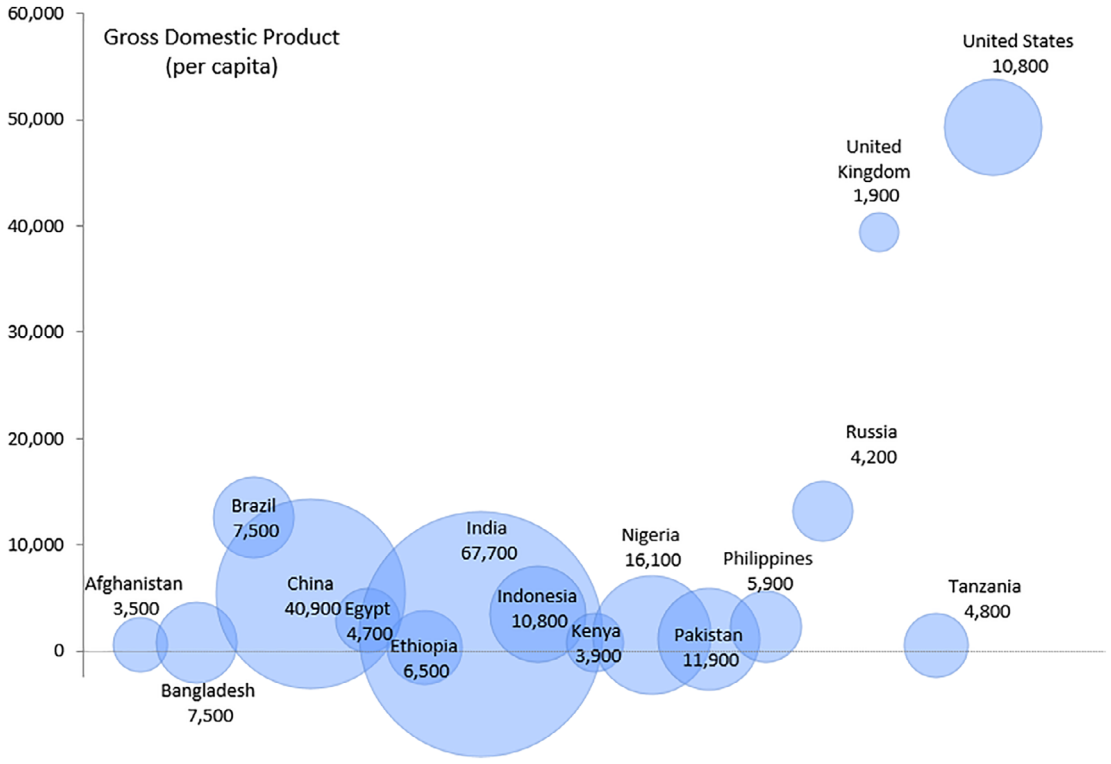

FIGURE 5 Estimated number of babies born with severe congenital heart defects (birth prevalence, 2.5 per 1,000) in selected countries, by per capita gross domestic product. The countries depicted account for over 60% of all births worldwide. Area of the circles are proportional to the number of affected babies. Data from Unicef and World Health Organization, 2011 from Botto (2015)

CHD caused in the order of 260,000 deaths in 2017, of which 180,000 (or just over two-thirds) were among children younger than 1 year (G. B. D. Congenital Heart Disease Collaborators, 2020).

Excess mortality does not end in early childhood, but extends for many decades in adult life (Olsen, Christensen, Pedersen, Johnsen, & Hjortdal, 2010) (Gilboa, Salemi, Nembhard, Fixler, & Correa, 2010).

Much of the impact is driven by relatively few severe types of CHD, including hypoplastic left heart syndrome, conotruncal defects, and atrioventricular septal defects (Boneva et al., 2001). This finding further underscores the importance of monitoring, preventing, and treating the subset of severe CHD.

3.2 | Evidence

The evidence is compelling that CHD outcomes can be improved with better care—starting from earlier diagnosis (including prenatally and through newborn screening) through improved medical and surgical management. The evidence is reflected in observed increasing survival in countries where such improvements have taken place. In this necessarily brief outline, the discussion about evidence will therefore focus mostly on primary prevention—the first element of the causal chain—because progress has been slower.

Clearly, to maximize primary prevention, and consequently to increase the odds that a baby is born healthy and with a normal heart, one must identify modifiable risk factors, and find ways to intervene effectively. Genes, environment, and probably chance, all contribute to CHD risk. "Strong" genetic causes (e.g., chromosomal anomalies, pathogenic gene variants in Mendelian conditions) remain to this day a significant challenge for primary prevention. The genetic contribution to CHD has been extensively reviewed, including in a series of 11 chapters in a recent book (see Sections 3 and 4 in of a recent book (Muenke, Kruszka, Sable, & Belmont, 2015)). Primary prevention can be envisioned for some (e.g., early education and later genetic counseling to address maternal age and consanguinity) but probably a minority. Numerically, chromosomal anomalies, mostly the common trisomies and deletion 22q11, account for an estimated 10–15% of CHD cases (Hartman et al., 2011). This contribution varies considerably by CHD type. For example, only a small fraction of hypoplastic left heart syndrome and d-transposition of the great arteries are associated with chromosomal anomalies (Hartman et al., 2011), leaving open the possibility that many of these cases might be amenable to primary prevention. De novo mutations and copy number variants might account for a fairly high fraction of cases, 10% of cases (Al Turki et al., 2014; Zaidi et al., 2013), and 5% (Warburton et al., 2014), respectively, suggesting that the proportion of cases due to all (strong) genetic factors combined—including chromosomal anomalies—could be at least 30%. A yet unclear fraction of the remaining CHD cases is likely to have a genetic component, perhaps as susceptibility genotypes in association with chance or some environment exposure. This area of active study will undoubtedly provide important evidence in the years to come and may refine both personal and population approaches to primary prevention. Finally, one should note that such estimates are lacking for much of the world, especially low and middle-income countries. The genetic workup of CHD requires a systematic approach, specific diagnostic technologies, and genetic professionals (medical geneticists, genetic nurse practitioners, and genetic counselors) working with cardiologists (Kruszka, Sable, Belmont, & Muenke, 2015). The scarcity of such resources likely drives the under-appreciation of the burden of genetic conditions for CHD in large areas of the world.

Returning to environmental or maternal modifiable factors, it is important to appreciate the value of critical review of the evidence, as not all epidemiologic association are causal. As a basis for interventions, some quantitative elements of the evidence are particularly important, such as specificity (what heart defect[s] does the exposure cause?), magnitude of risk (how high is the risk if exposed?), and frequency of exposure in the population (how common is it among the at-risk population such as women of childbearing age?). As an illustration, Table 1 presents a few examples of risk factors for CHD together with selected data relevant to decision-making.

Among these elements, one that is sometimes overlooked or underappreciated is the attributable fraction of disease associated with an exposure (Column 5 from the left). This metric (Williamson, 2010) uses as inputs the relative risk of disease and the frequency of the exposures (Columns 3 and 4 in the table), and generates estimates of the *number of cases that would be prevented* if the exposure is removed (Column 5). Whereas the relative risk of disease is probably a biologic universal and fairly similar across most populations, the frequency of exposures (e.g., smoking, obesity) can vary dramatically. As a consequence, the number of preventable cases for a given exposures will also vary significantly. Note that even "weak" risk factors (e.g., smoking in Table 1, with a relative risk of only 1.1.) can cause many cases of disease in a population, if common enough.

This dependence of the number of affected cases on exposure rates underscores the importance of *surveillance* of risk factors—the first element of triple surveillance—and specifically, the importance of tracking exposure rates *in the population and over time*. Some such programs already exist but they are few and tend to operate in isolation from the other elements of the causal chain. Examples include the PRAMS program in the United States (Centers for Disease Control and Prevention, n.d.; D'Angelo et al., 2007) and the STEPS program of the World Health Organization (World Health Organization, 2020).

Ideally, data on risk factors, the evidence for causality, relative risk, and exposure frequency in the population and number of cases potentially caused would be compiled, updated and made available regularly, so each country could look at the potential contribution of different risk factors to CHD cases in *their* population. To facilitate an evidence-based approach to population interventions. Much of the basic data are already available is several reviews on CHD risk factors (Botto, 2013; Jenkins et al., 2007; Riehle-Colarusso & Patel, 2014). The major gap is the lack of timely and accurate data on the frequency of risk factors by country and within relevant subgroups (e.g., women of childbearing age, ideally also stratified by key sociodemographic variables), information that can help developed global as well as targeted primary prevention interventions.

A final point deserving emphasis is the potential for additional prevention beyond CHD (Table 1, rightmost column). Many risk factors for CHD are also risk factors for other adverse pregnancy outcomes as well as health outcomes in mother (and father). Examples include smoking, diabetes, folate insufficiency, unhealthy nutritional status (obesity and underweight). These factors can increase the risk

TABLE 1 Examples of risk factors for congenital heart disease (CHD), their frequency, and potential benefits of prevention

Factor	Evidence for causation	Relative risk[a]	Typical frequency of exposure[b]	Number of preventable cases[c] among 1 million births	Additional prevention[d]
Diabetes (pregestational)	Definite	3.8	+++ (1–6%)	Frequency of exposure = 3% Number of preventable CHD cases = 620 (21 with hypoplastic left heart s.)	Definite (birth defects, many other pregnancy outcomes)
Obesity (BMI > 30)	Probable	1.2	+++ (~15–25% variable and increasing)	Frequency of exposure = 25% Number of preventable CHD cases = 435 (32 with hypoplastic left heart s.)	Definite (preterm birth, other birth defects)
Smoking	Possible	1.1	+++ (variable: From very low to 10–20%)	Frequency of exposure = 20% Number of preventable cases = 172 (61 with atrioventricular canal)	Definite (orofacial clefts, preterm birth, low birth weight
Fever/flu	Possible	2.1	+++ (6–10%)	Frequency of exposure = 7% Number of preventable CHD cases = 562	Probable (neural tube defects)

[a]Approximate relative risk for all CHD combined.
[b]+ to +++ indicate relative frequency, with comment and range of estimates from different countries in parenthesis.
[c]Estimates of potentially preventable cases among 1 million births, if the risk factor frequency among women of childbearing age is reduced to zero from the stated baseline frequency. Additional assumptions for calculation of preventable cases: birth prevalence for CHD overall, 80 per 10,000; for HLHS, 2.8 per 10,000; for atrioventricular canal, 9.4 per 1000. All calculations assume that the association reflected in the relative risk is causal.
[d]Additional adverse health outcomes that would benefit by removing the risk factor. The examples focus on pregnancy outcomes, but in all cases the health of the mother also will benefit.

for other congenital anomalies, low birth weight, preterm birth, and maternal disease. Highlighting such evidence can provide even stronger incentives for collaborative action across multiple partners with support from a broader base of stakeholders.

3.3 | Strategies

With incentives and evidence in place, the key issue becomes one of strategy: how to maximize prevention given available resources, competing needs, and the local context of social, cultural, and health care system factors. Only a few simple points will be noted here. First, effective population interventions often include partnerships of groups that may focus on different outcomes but on similar risk factors. Second, effective strategies (for primary prevention in particular) focus on preconception health, rather than on pregnancy alone. By the time a pregnancy is recognized, the opportunity for primary prevention is largely lost. The heart starts developing early in pregnancy, beating rhythmically from about 21 days postfertilization (Gittenberger-de Groot, Bartelings, Poelmann, Haak, & Jongbloed, 2013). However, prenatal visits, when screening and pregnancy care with a health provider typically begins, often occur from several weeks to months after the last menstrual period, too late to prevent CHD and most other congenital anomalies. Even starting very early in pregnancy may be too late, because for many chronic conditions such as maternal diabetes or phenylketonuria, restoring a healthy maternal environment takes time. In addition, many pregnancies, at least half in the United States and probably most pregnancies worldwide, are unplanned. Thus, to ensure maximal prevention for the largest population, women's health and environmental health must be promoted and supported needs through the lifespan.

Finally, effective global interventions often combine individual-level and population interventions, ideally across the lifespan (Botto, 2013; Jack et al., 2008). A powerful strategic framework for such interventions is the health impact pyramid (Frieden, 2010). This framework emphasizes the value of integrating broad based, long-lasting societal intervention with individual-level practices. It also makes the practical point that the less effort is required of an individual, the more likely the intervention will be long-lasting, ongoing, and cost-effective. Maternal diabetes provides a clear example. Maternal diabetes is an established and strong risk factor for congenital heart defects (Lisowski et al., 2010), as well as for many other fetal and maternal adverse effects (Inkster et al., 2006; Wahabi, Alzeidan, Bawazeer, Alansari, & Esmaeil, 2010; Wahabi, Alzeidan, & Esmaeil, 2012). The evidence is strong, qualified, and quantified—reviews and meta-analyses have generated fairly robust risk estimates for several types of CHD (Correa et al., 2008; Lisowski et al., 2010), and have also shown that preconception care aimed at reestablishing metabolic control before conception reduces significantly the risk for congenital anomalies as well as for other adverse fetal and infant outcomes (Wahabi et al., 2010; Wahabi et al., 2012). Maternal pregestational diabetes is also fairly common among women of childbearing age and increasing in several countries (Table 1). For these reasons, maternal diabetes is a high value target for primary prevention—with potential benefits expanding well beyond CHD.

Applying the Health Impact Pyramid framework to diabetes (Figure 6) highlights the opportunities and challenges of interventions aimed at reaching the entire population at risk.

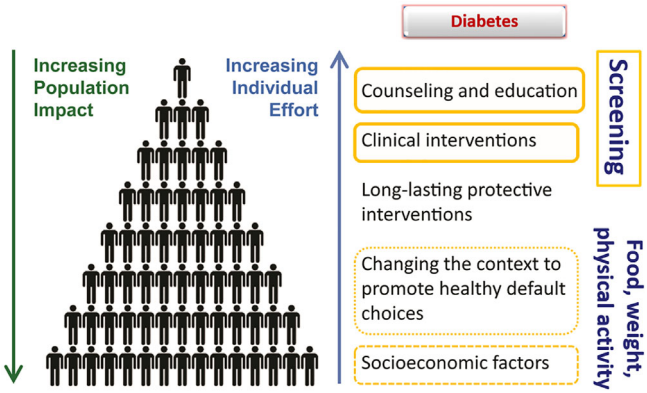

FIGURE 6 Health impact pyramid: integrating interventions to reduce diabetes-related risk for congenital heart defects and other adverse fetal and maternal outcomes

Clinical interventions, including diabetes screening, counseling, and interventions are effective. However, they are also costly, intensive, and require considerable effort on the part of women and health providers. As a consequence, these individual-level interventions typically reach only part of the population at risk, often the more affluent and educated. Population coverage is incomplete, and the risk for health disparities is high. However, integrating these efforts with population-wide interventions that influence the broader social and economic determinants of health can support wider and more effective prevention while reducing disparities. Such additional broad-based interventions may require wide-ranging policy and education initiatives, such as investing in schools (e.g., with better education, food programs, and exercise opportunities) and work (e.g., incentives for physical activity, weight control, and health screenings). This broad approach, by also reducing individual effort (e.g., food programs that make the healthy choice the default choice), can provide greater overall impact and long-lasting effects.

3.3.1 | Reinterpreting CHD knowledge for action: Interim conclusions

Arguably, currently available data on CHD, whether directly obtained or estimated, is spotty and incomplete, especially but not only in low and middle-income countries. Yet, the framework of the causal chain can help reinterpret available knowledge to promote action for better prevention and care. One way to present and use the data are through the triple lens of incentive, evidence, and strategy. Articulating an activist message through critically reviewed information that highlighting the evidence as well as the gap helps emphasize the cost of inaction as well as the benefits of action. Such a message in the hands of stakeholders can become a powerful voice for change.

The next question becomes how to fill the critical gaps in knowledge that hinder progress in prevention and care. The framework of the causal chain provides yet another starting point.

4 | GENERATING NEW CHD KNOWLEDGE FOR ACTION

The framework of the causal chain (Figure 1) is embedded in "triple surveillance"—the integrated system that tracks in a population the three domains of cause, occurrence, and outcomes. The goal of triple surveillance is to support population-wide prevention and care through reliable and timely data. Triple surveillance has been advocated for neural tube defects as well as for congenital anomalies in general and rare diseases (Botto & Mastroiacovo, 2018a; Botto & Mastroiacovo, 2018b), and is here discussed specifically in the context of CHD.

One must acknowledge at the outset the criticism that at critics that such health surveillance is largely unnecessary, too complex to succeed in low resource countries, and a drain on resources that are best focused solely on interventions. Such criticism should not be disregarded. In fact, surveillance can become overly complex and does require resources. In addition, well-designed prevention interventions will likely have some beneficial effects, with or without health surveillance. Yet, the view that surveillance is unrealistic and unnecessary is simplistic and risky. In the absence of population health surveillance, interventions risk not living up to their full potential, mistakes are repeated, good intentions flounder, and opportunities for improvement are lost. By not investing in efficient surveillance, intervention may end up costing more and doing less than they would otherwise.

One way to understand and communicate the value of surveillance is to highlight how data from population health surveillance provide answers to key questions that individuals and communities have when confronted with the reality of CHD in their midst (Table 2). In fact, health surveillance data complement and complete the information that clinicians try to give individual patients and families, one at the time.

As reframed in the table, ultimately the main questions of families and patients—what is this? What will happen now? Why did it happen?—also have a societal dimension that needs answers as well. Tracking the three domains of causes, occurrence, and outcomes will provide information that benefits the community in addition to the individual—addressing for example issues such as disparities (both in exposures and outcomes), access to care, and prevention priorities.

Some countries have health tracking systems that address one or the other of the three domains of the causal chains. However, often the systems are separate and are operated by organizations with different goals and priorities, with few if any established links. That such triple surveillance is not fully realized even where the health infrastructure is well-developed and resources are abundant suggests that resources are one but not the only or even the main issue, but perhaps the prevalent operating culture is—incomplete appreciation of potential synergies, challenges in data sharing, and perhaps habit (the way things have always been done).

4.1 | Potential added value of triple surveillance

Classic CHD surveillance, which typically focuses on CHD occurrence (mostly at birth), provides many benefits where it is deployed, mainly

TABLE 2 Clinical and public health approaches to answering three key questions of family and community when confronted with congenital heart disease

Question	Key theme	Clinical issues/approaches	Public health issues/approaches
What is this?	Diagnosis	Often the first question of families. Initially suspected either prenatally, or after birth by clinical exam or newborn screening (pulse oximetry). Diagnosis typically requires specialty expertise and echocardiography, leading to many missed cases or misdiagnoses where such skills and resources are scarce. Data from single hospitals or network may not represent an area's true burden of disease (e.g., in areas with many home births).	A basic public health question: How many are affected in the population and who are they? In the framework of triple surveillance, CHD occurrence is the middle component of triple surveillance: The consequence of risk factors and in turn the antecedent of health outcomes. Public health approaches to diagnosis include population-wide newborn screening coupled to key data collection. A major goal is to reduce health disparities in diagnosis and care, though challenges related to diagnostic resources remain By integrating, strengthening, and streamlining local data systems (e.g., neonatal and pediatric health surveillance, hospital discharge, vital records), health surveillance provides a more truthful picture of the affected population
What will happen now?	Outcomes	Typically the next question after the diagnosis In-hospital and short term follow up can generate high quality information on early mortality and morbidity, some of which may depend on highly granular clinical data (e.g., whether the CHD is isolated vs. with multiple congenital anomalies vs. syndromic). Long-term follow however is typically challenging, with increasing loss of follow up beyond the immediate medical and surgical urgency. Factors include population mobility, access to care, and disengagement from specialized care.	Outcomes represent a population's the true burden of disease, and its assessment is the third component of triple surveillance: The ultimate consequence of a population's burden of risk Population-level information may be limited in depth but may have broader breadth, in both space and time—with wider geographic coverage and longer time horizon. By doing so, it can help identify and track differences and preventable disparities in outcomes (e.g., mortality, morbidity, disability) linked to geography, sociodemographic, and other factors By strengthening and linking multiple data sources, public health surveillance can provide the community and health provider a more complete and compelling view of the true burden of disease in both the short and long term. However, the quality of surveillance data depends on the quality of the primary data sources. Also, to be valuable, surveillance information should be timely, useful to clinicians and policy makers, and ongoing
Why did it happen and will it happen again?	Cause and risk	Eventually this question will arise in the clinic. If not, it should be elicited in counseling because of frequent feelings of guilt on the part of parents, and because families may overestimate the risk for recurrence, which in CHD is often much lower than classic Mendelian risks. Clinical and genetic assessment can provide information on potential causes, genetic (e.g., deletion 22q11) and environmental. Especially in the case of likely environmental causes (e.g., maternal diabetes), counseling can lead to recurrence prevention (e.g., improved preconception health).	On a community basis, this question directly relates to the risk factor profile of the population, the root cause of the occurrence of CHD and the first component of triple surveillance. A comprehensive and timely summary of a population's risk factor profile for CHD is currently unavailable for many if not all countries, highlighting a major gap in actionable data. Knowing the frequency of risk factors in a population together with the associated CHD risks (e.g., the population frequency of maternal diabetes with the relative risk of CHD with maternal diabetes) allows to estimate the number of CHD cases in the population that are due to the risk factors, and thus are in principle preventable by removing the risk factor. These numbers help visualize the potential of prevention as well as the ongoing burden of inaction, a key data element for action.

in terms of awareness. However, expanding health surveillance through the causal chain can provide significant additional benefits but explicitly focusing on data for primary prevention and care. To summarize (Figure 1), the three components of this approach are (a) surveillance of selected established risk factors for CHD in the population (b) surveillance of CHD occurrence; and (c) surveillance of longitudinal health outcomes among those affected.

The value of such system depends critically on connection and focus—the extent to which the three components "speak to each other" and "speak about the same people," that is, track the same population. For example, capturing disease outcomes (in addition to disease occurrence) provides an extremely important measure of the success of prevention—fewer deaths, healthier lives, and better function. As emphasized previously, disease occurrence combined with health outcomes provide a more truthful assessment of burden of disease and how it changes over time, thus reflecting also the quality of care. Timeliness is also improved. For example, one can directly and quickly assess the success of interventions aimed at reducing the

TABLE 3 Modalities, benefits, and challenges in triple surveillance of congenital heart disease

Focus	Goals and modalities	Benefits/issues/challenges
Risk factor profile	Why How: Population surveys Specials studies	Estimates the population's burden of risk, helps identify high value intervention opportunities, track successes and remaining gaps Population surveys on risk factors for CHD often already conducted outside of CHD-related activities—For example, surveys of diabetes, smoking, or nutritional status may not systematically report information on women of childbearing age, but they still might have such data to mine In the absence of ongoing population surveys, information from special studies may provide useful initial assessment—For example, control groups in well conducted case control studies of risk factors for non-CHD outcomes can still provide estimates of risk factor frequency in the population
CHD occurrence	Why How: Case finding How: Ascertainment How: Coding/ classification	Directly assesses birth prevalence, the major immediate determinant of burden of disease Typical modalities include single vs. single source. Best results if sources are multiple with complementary data. Examples include prenatal centers, birth centers, home health/birth attendant services, specialty clinics, labs (e.g., genetic labs for syndromic diagnoses) *Expanding prenatal detection, newborn screening, and telemedicine have transformative potential in improving detection rates* Once detected at the point of care, this information needs to be ascertained by the surveillance program. Common modalities include active (program staff accesses sources to retrieve data) versus passive (sources provide data centrally) versus hybrid systems (program staff accesses key sources, with additional sources providing data centrally) Active ascertainment is effective but costly; passive cost less but data may be comparatively less complete, accurate and timely; *in many cases, especially in low resource settings, hybrid systems with local "champions" may provide the best value in terms of data quality* vs. *cost* ICD10 useful but limited detail; HPO terms more detailed; CHD specific systems best (e.g., STS-Society of Thoracic Surgeons; IPCCC-international Pediatric and congenital cardiac code) but not used in many standard data sources (e.g., hospital discharge data) *Best done through clinical case review by experts*
CHD outcomes	Why: How: Focused core data and longitudinal follow up	Directly assesses the true burden of disease (mortality, morbidity, disability, quality of life) on individuals, their families, and the community. In doing so, it measures the true value of optimal prevention and care Generating useful and valid longitudinal health outcome data is challenging even in high resource settings. However, there is likely much waste and insufficient clinical and public health focus in much data collection (e.g., excessive focus on administrative priorities, "recreational data collection"). Goal is to focus on a core set of data that is useful clinically, integrate available information systems (clinical and administrative), and streamline activities (eliminating overlapping surveillance programs, paring down data collection, prioritizing data quality and timeliness). Paradoxically, better systems can be developed in lower resources area, where streamlining, integration, and operational "waste" can be built from the group up (vs. re-engineering the fragmented and often inefficient data systems developed over decades in high resources countries)

Abbreviations: ICD, international classification of diseases; HPO, human phenotype ontology; CHD, congenital heart disease.

TABLE 4 Overall framework and operational innovations for improved surveillance of congenital heart disease (CHD)

Proposal	Why	Crucial and potentially overlooked issues
A. Overall strategies		
Focus on what matters	If starting and if resources are limited, focus first on major severe congenital heart disease, which drive much of the health burden associated with CHD Be selective about collecting data—Focus on what is useful and meaningful for action, avoid "recreational data collection"	Severe CHD are comparatively easier to detect, including with newborn screening, and present earlier, but can be missed in out of hospital deaths (home births or after early discharge from the birthing center) Each piece of data has a cost: Choose what to collect to answer specific questions that can move forward clinical care, prevention, and population health
Focus on quality	Because information is for action, it must be reliable—complete, accurate, and timely. Bad data may be worse than no data	Quality does not come automatically. It must be built into a system, through teamwork, shared standard operating procedures, checklists, and other means of embedding quality into each process of the system.
Use what is available	Existing programs, even if not directly related to CHD, may support activities targeted at better care and prevention of CHD, either immediately or with minor enhancements	Programs conducting relevant surveys (e.g., nutrition, diabetes, lifestyle factors, immunizations) and surveillance (e.g., perinatal health, adult health), can be mined or adapted for CHD-related purposes. Such efficiencies are important everywhere, and especially crucial in low resource settings.
Integrate surveillance into the clinical workflow	Timeliness and quality can quickly degrade if public health surveillance is separate and disconnected from clinical workflow. However, this is precisely what happens (and has happened) for decades in many areas, leading to wasted resources (because of inefficiencies) and wasted data (because not used)	Incorporating core information on CHD occurrence and outcomes into easily extracted data variables from existing systems (e.g., discharge summaries, perinatal and pediatric health surveillance) streamlines data collection and promotes timeliness and accuracy in the data
Develop a practical and robust sampling frame for large populations	Population-based surveillance for an entire large country (e.g., India) is extremely challenging, and the data produced may not be complete or accurate. A sample of small areas rigorously chosen to be representative of the larger region and population(s) can provide reliable, high-quality data at a fraction of the cost	Sampling of population-based area surveillance has been used in other contexts (e.g., immunizations and nutrition) to obtain good-quality information with fewer limitations than convenience-based facility (hospital) programs, in particular in areas with in a large proportion of home births
Commit for the long term	Good programs take time to work and take root: Surveillance is meaningful if ongoing and sustainable	Commitment also includes clinical training and development of epidemiologic capacity—Critical for conditions as complex as CHD- -
B. Operational improvements and innovations		
When tracking CHD occurrence, include all pregnancy outcomes	Stillbirths and pregnancy terminations are a significant "hidden" toll of many congenital anomalies, including congenital heart defects.	Stillbirths and terminations of pregnancy are very often undetected, unexamined, and underreported. This challenge may increase with better and more widespread prenatal diagnostics
Promote newborn screening	Newborn screening has to the potential to increase CHD detection at birth, crucially important for clinical care and for epidemiologic surveillance	To be more generally useful, key information on newborn screening (e.g., whether testing was done and the result) must be incorporated in a data system, so it can be used to track and improve this important clinical and public health program

(Continues)

TABLE 4 (Continued)

Proposal	Why	Crucial and potentially overlooked issues
Track health outcomes over time on a population basis	Because many severe CHD have treatments but not necessarily cures, the burden of disease must be tracked over time, well beyond the newborn period and infancy	Information on the lifelong burden of CHD is scarce or completely lacking, but is the key metric of the true burden of disease, reflecting both the quality of prevention and the quality of care. Generating accurate longitudinal information is extremely challenging even in high resource countries, and requires significant investments in longitudinal linkages and a lifelong specialized care
Track established risk factors of CHD occurrence	Although not all causes of CHD are known, there is already a firm understanding on a few modifiable risk factors that if removed will prevent many cases of CHD. However, in many areas, tracking CHD occurrence is disconnected from tracking CHD risk factors (when the latter even occurs).	Because many risk factors for CHD (e.g., diabetes, smoking) are also risk factors for other diseases and adverse health outcomes, CHD-focused programs will benefit by connecting and linking with such programs to mine available data and, if necessary, help improve those programs so they become more useful to the community of people with CHD. For example, the World Health Organization's STEPS and the CDC's PRAMS programs already collect (for many other purposes) information on common disease risk factors

risk factors by tracking the risk factor itself well before such success translates in reductions in the final outcomes. For example, the effectiveness of campaigns to lower maternal pregestational diabetes or smoking can be assessed more quickly and directly by tracking the frequency of those exposures among women of childbearing age versus waiting for changes in the occurrence of the associated congenital anomalies (some CHD, neural tube defects, etc.). In fact, rate changes of rare conditions may be difficult to detect quickly in small populations. Nevertheless, disease occurrence and health outcomes must be tracked as well, to ensure that no other downstream has negated the effect of the reduction in risk factor prevalence.

4.2 | Challenges and opportunities for implementation

The challenges to implementation must not be underestimated. Some challenges are operational—for example, related to cost, organization, data systems, and training—others, as noted, may be cultural—related to the challenges of integrating systems and cultures. The challenges need to be recognized and addressed, ideally by teams that include clinicians (especially front-end workers such as nurses and physicians), epidemiologists, data analyses, and administrators. A focused and realistic assessment of potential pitfalls and required skill sets can help willing partners move forward effectively (Table 3).

For example, the risk factor profile of a population can be developed through partnerships with organizations for whom CHD is far from being a priority, but do track data on common risk factors (e.g., diabetes or smoking). Tracking CHD occurrence and outcomes, on the other hand, requires close collaboration between the clinical and public health communities, to minimize redundant data collection and focus on information that are both of clinical and public health relevance ("no recreational data collection"). Based on experience on health surveillance of many other congenital conditions, some overall strategies and approaches should be considered (Table 4).

For example, it is critical to have clear goals, and focus on what matters, both in terms of CHD (e.g., which conditions to monitor) and the core (minimal) data elements to be collected. Integrating with partners with overlapping reach and interest (e.g., perinatal health surveillance systems) can accelerate and simplify implementation, especially if some elements are already in place ("use what is available"). Especially in low resource areas, one must resist the temptation to create a freestanding public health surveillance systems disconnected from clinical operation. Ideally, each data element collected by health surveillance (e.g., on occurrence, morbidity, and mortality) has value not only for public health but also for clinicians involved in prevention and clinical care. Each piece of data has a cost, and if collected it must be used. Such broad guidelines and approaches must be adaptable, so they are practical, scalable, and effective in low resource settings, where most of the births occur worldwide. Important population and contextual factors to consider in planning phase include the proportion of home births, the availability and use of prenatal diagnosis and pregnancy terminations, and the existing systems or activities such as nutrition and risk factor surveys, other health surveillance programs, and the availability of vital records.

Restricted resources may spur innovative thinking—and help focus on what is essential for the overarching goal of improved health outcomes. Focusing on the essentials can also speed deployment, lower cost, and improve data quality. In addition, strategies such as sampling can improve efficiencies by focusing limited resources to selected areas in highly populated countries. If appropriately done, sampling can generate high quality information—complete, accurate, and timely—that may be generalized to other areas in the country.

Finally, especially in low resource settings, it is helpful to implement the system gradually, ideally with an initial pilot—for example, beginning in one area, and focusing on a few carefully chosen established risk factors relevant to that population (e.g., selected on the basis of potential attributable fraction or community concerns), some severe CHD, and few basic outcome measures (e.g., neonatal and infant mortality). Once the system is operational and successful, it can be expanded to larger areas, more risk factors, and additional outcomes.

5 | CONCLUSIONS

CHD is already a global challenge and will be increasingly so as more countries improve their neonatal and infant mortality through better infection control and prenatal and perinatal care. Because of this "epidemiologic transition," the impact of CHD and other congenital anomalies in the population will continue to increase. Addressing these challenges effectively on a population-wide level requires being able to generate reliable and timely data on an ongoing basis—a core function of population health surveillance.

To accelerate the dual goal of better primary prevention and better care, innovation is needed. Triple surveillance, envisioned as innovative population health surveillance that concurrently tracks and integrated data about causes, disease occurrence, and health outcomes, can be part of that innovation. The data can be used to highlight disease burden—the incentive for action—and to evaluate the success or gaps in interventions—the effectiveness of strategies.

Crucial elements in triple surveillance include integration, adaptability, and focus. Each component may provide some information, but the whole picture emerges only when integrated, the real synergies occur when integrated. The system must be tailored to local needs, resources, and priorities—and by appropriately streamlining operations, avoiding duplications, and leveraging common interests and goals, such systems should be doable nearly everywhere. Finally, focus is crucial—focus on what matters and what can make a difference in prevention and care throughout the population. In fact, a broader benefit of implementing such a system may well be cultural—a closer integration between clinical care and public health for the common goals of prevention and care. Perhaps this cultural change may be difficult to measure, but can have long-lasting benefits globally.

ORCID

Lorenzo D. Botto https://orcid.org/0000-0002-5322-7116

REFERENCES

Al Turki, S., Manickaraj, A. K., Mercer, C. L., Gerety, S. S., Hitz, M. P., Lindsay, S., … Hurles, M. E. (2014). Rare variants in NR2F2 cause congenital heart defects in humans. *American Journal of Human Genetics*, *94*(4), 574–585.

Boneva, R. S., Botto, L. D., Moore, C. A., Yang, Q., Correa, A., & Erickson, J. D. (2001). Mortality associated with congenital heart defects in the United States: Trends and racial disparities, 1979-1997. *Circulation*, *103*(19), 2376–2381.

Botto, L. D. (2013). Epidemiology and prevention of congenital heart defects. In H. D. Allen, D. J. Driscoll, R. E. Shaddy, & T. F. Feltes (Eds.), *Moss and Adams' heart disease in infants, children, and adolescents, including the Fetus and young adult* (8th ed.). Philadelphia: Lippincott.

Botto, L. D. (2015). Epidemiology and prevention of congenital heart defects. In K. Muenke & B. Sable (Eds.), *Congenital heart disease: Molecular genetics, principles of diagnosis and treatment*. Basel (Switzerland): Karger.

Botto, L. D., & Mastroiacovo, P. (2018a). From cause to care: Triple surveillance for better outcomes in birth defects and rare diseases. *European Journal of Medical Genetics*, *61*(9), 551–555.

Botto, L. D., & Mastroiacovo, P. (2018b). Triple surveillance: A proposal for an integrated strategy to support and accelerate birth defect prevention. *Annals of the New York Academy of Sciences*, *1414*(1), 126–136.

Boulet, S., Grosse, S. C., Riehle-Colarusso, T., & Correa-Villasenor, A. (2010). Health care costs of congenital heart defects. In D. F. Wyszynski, A. Correa-Villasenor, & T. P. Graham (Eds.), *Congenital heart defects: From origin to treatment* (pp. 493–501). New York: Oxford University Press.

Centers for Disease Control and Prevention. PRAMS: Pregnancy Risk Assessment Monitoring System.

Centers for Disease Control and Prevention (CDC). (2010). Racial differences by gestational age in neonatal deaths attributable to congenital heart defects — United States, 2003–2006. *MMWR. Morbidity and Mortality Weekly Report*, *59*(37), 1208–1211.

Centers for Disease Control and Prevention, Waitzman, N. J., Romano, P. S., Scheffler, R. M., & Harris, J. A. (1995). Economic costs of birth defects and cerebral palsy – United States, 1992. *MMWR. Morbidity and Mortality Weekly Report*, *44*(37), 694–699.

Christianson, A., Howson, C. P., & Modell, B. (2006). *March of Dimes global report on birth defects: The hidden toll of dying and disabled children*. White Plains, New York: March of Dimes Birth Defects Foundation.

Correa, A., Gilboa, S. M., Besser, L. M., Botto, L. D., Moore, C. A., Hobbs, C. A., … Reece, E. A. (2008). Diabetes mellitus and birth defects. *American Journal of Obstetrics and Gynecology*, *199*(3), 237 e231–237 e239.

D'Angelo, D., Willians, L., Morrow, B., Cox, S., Harris, N., Harrison, L., … Zapata, L. (2007). Preconception and Interconception health status of women who recently gave birth to a live-born infant — pregnancy risk assessment monitoring system (PRAMS), United States, 26 reporting areas, 2004. *MMWR Surveillance Summaries*, *56*(10), 1–35.

Dolk, H., Loane, M., & Garne, E. (2011). Congenital heart defects in Europe: Prevalence and perinatal mortality, 2000 to 2005. *Circulation*, *123*(8), 841–849.

Frieden, T. R. (2010). A framework for public health action: The health impact pyramid. *American Journal of Public Health*, *100*(4), 590–595.

G. B. D. Congenital Heart Disease Collaborators. (2020). Global, regional, and national burden of congenital heart disease, 1990–2017: A systematic analysis for the global burden of disease study 2017. *Lancet Child Adolesc Health* pii: S2352-4642(2319)30402-X.

Gilboa, S. M., Salemi, J. L., Nembhard, W. N., Fixler, D. E., & Correa, A. (2010). Mortality resulting from congenital heart disease among children and adults in the United States, 1999 to 2006. *Circulation*, *122*(22), 2254–2263.

Gittenberger-de Groot, A. C., Bartelings, M. M., Poelmann, R. E., Haak, M. C., & Jongbloed, M. R. (2013). Embryology of the heart and

its impact on understanding fetal and neonatal heart disease. *Seminars in Fetal & Neonatal Medicine*, *18*(5), 237–244.

Hartman, R. J., Rasmussen, S. A., Botto, L. D., Riehle-Colarusso, T., Martin, C. L., Cragan, J. D., … Correa, A. (2011). The contribution of chromosomal abnormalities to congenital heart defects: A population-based study. *Pediatric Cardiology*, *32*(8), 1147–1157.

Inkster, M. E., Fahey, T. P., Donnan, P. T., Leese, G. P., Mires, G. J., & Murphy, D. J. (2006). Poor glycated haemoglobin control and adverse pregnancy outcomes in type 1 and type 2 diabetes mellitus: Systematic review of observational studies. *BMC Pregnancy and Childbirth*, *6*, 30.

Jack, B. W., Atrash, H., Coonrod, D. V., Moos, M. K., O'Donnell, J., & Johnson, K. (2008). The clinical content of preconception care: An overview and preparation of this supplement. *American Journal of Obstetrics and Gynecology*, *199*(6 Suppl 2), S266–S279.

Jenkins, K. J., Correa, A., Feinstein, J. A., Botto, L., Britt, A. E., Daniels, S. R., … Webb, C. L. (2007). Noninherited risk factors and congenital cardiovascular defects: Current knowledge: A scientific statement from the American Heart Association Council on cardiovascular disease in the young: Endorsed by the American Academy of Pediatrics. *Circulation*, *115*(23), 2995–3014.

Keren, R., Luan, X., Localio, R., Hall, M., McLeod, L., Dai, D., … Pediatric Research in Inpatient Settings N. (2012). Prioritization of comparative effectiveness research topics in hospital pediatrics. *Archives of Pediatrics & Adolescent Medicine*, *166*(12), 1155–1164.

Kruszka, P., Sable, C. A., Belmont, J. W., & Muenke, M. (2015). The genetic workup for congenital structural heart disease: From clinical to genetic evaluation. In M. Muenke, P. Kruszka, C. A. Sable, & J. W. Belmont (Eds.), *Congenital heart disease: Molecular genetics, principles of diagnosis and treatment* (pp. 238–268). Basel (Switzerland): Karger.

Lisowski, L. A., Verheijen, P. M., Copel, J. A., Kleinman, C. S., Wassink, S., Visser, G. H., & Meijboom, E. J. (2010). Congenital heart disease in pregnancies complicated by maternal diabetes mellitus. An international clinical collaboration, literature review, and meta-analysis. *Herz*, *35*(1), 19–26.

Lopez, A. D., & Mathers, C. D. (2006). Measuring the global burden of disease and epidemiological transitions: 2002-2030. *Annals of Tropical Medicine and Parasitology*, *100*(5), 481–499.

Marelli, A. J., Mackie, A. S., Ionescu-Ittu, R., Rahme, E., & Pilote, L. (2007). Congenital heart disease in the general population: Changing prevalence and age distribution. *Circulation*, *115*(2), 163–172.

Muenke, M., Kruszka, P., Sable, C. A., & Belmont, J. W. (2015). *Congenital heart disease: Molecular genetics, principles of diagnosis and treatment*. Karger.

Olsen, M., Christensen, T. D., Pedersen, L., Johnsen, S. P., & Hjortdal, V. E. (2010). Late mortality among Danish patients with congenital heart defect. *The American Journal of Cardiology*, *106*(9), 1322–1326.

Riehle-Colarusso T, Patel SS. 2014. Nongenetic risk factors for congenital heart defects. Congenital Heart Disease: Molecular Genetics, Principles of Diagnosis and Treatment.

Robbins, J. M., Bird, T. M., Tilford, J. M., Cleves, M. A., Hobbs, C. A., Grosse, S. D., & Correa, A. (2007). Hospital stays, hospital charges, and in-hospital deaths among infants with selected birth defects—United States, 2003. *MMWR. Morbidity and Mortality Weekly Report*, *56*(2), 25–29.

Rosano, A., Botto, L. D., Botting, B., & Mastroiacovo, P. (2000). Infant mortality and congenital anomalies from 1950 to 1994: An international perspective. *Journal of Epidemiology and Community Health*, *54*(9), 660–666.

Wahabi, H. A., Alzeidan, R. A., Bawazeer, G. A., Alansari, L. A., & Esmaeil, S. A. (2010). Preconception care for diabetic women for improving maternal and fetal outcomes: A systematic review and meta-analysis. *BMC Pregnancy and Childbirth*, *10*, 63.

Wahabi, H. A., Alzeidan, R. A., & Esmaeil, S. A. (2012). Pre-pregnancy care for women with pre-gestational diabetes mellitus: A systematic review and meta-analysis. *BMC Public Health*, *12*, 792.

Waitzman, N. J., Romano, P. S., & Scheffler, R. M. (1996). *The cost of birth defects* (p. 276). Lanham (Maryland, USA): University Press of America.

Warburton, D., Ronemus, M., Kline, J., Jobanputra, V., Williams, I., Anyane-Yeboa, K., … Levy, D. (2014). The contribution of de novo and rare inherited copy number changes to congenital heart disease in an unselected sample of children with conotruncal defects or hypoplastic left heart disease. *Human Genetics*, *133*(1), 11–27.

Warnes, C. A., Liberthson, R., Danielson, G. K., Dore, A., Harris, L., Hoffman, J. I., … Webb, G. D. (2001). Task force 1: The changing profile of congenital heart disease in adult life. *Journal of the American College of Cardiology*, *37*(5), 1170–1175.

Williamson, D. F. (2010). The population attributable fraction and confounding: Buyer beware. *International Journal of Clinical Practice*, *64*(8), 1019–1023.

World Health Organization. 2020. Sustainable Developmental Goals.

World Health Organization. STEPwise approach to surveillance (STEPS).

Zaidi, S., Choi, M., Wakimoto, H., Ma, L., Jiang, J., Overton, J. D., … Lifton, R. P. (2013). De novo mutations in histone-modifying genes in congenital heart disease. *Nature*, *498*(7453), 220–223.

How to cite this article: Botto LD. From cause to care: Can a triple approach to better population data improve the global outlook of congenital heart disease? *Am J Med Genet Part C*. 2020;184C:23–35. https://doi.org/10.1002/ajmg.c.31775