Latin American Collaborative Study of Congenital Malformations (ECLAMC): A Model for Health Collaborative Studies

F.A. Poletta[a, b]   J.A. Gili[a]   E.E. Castilla[a, b]

[a]ECLAMC (Estudio Colaborativo Latinoamericano de Malformaciones Congénitas) at Centro de Educación Médica e Investigaciones Clínicas (CEMIC) (CONICET), Buenos Aires, Argentina; [b]ECLAMC at INAGEMP (Instituto Nacional de Genética Médica Populacional), Rio de Janeiro, Brazil

Introduction

During the mid-sixties, the pandemic of congenital malformations produced by a new medication, thalidomide, stunned the world and triggered the creation of registries and surveillance systems in several countries, including Argentina. In 1967, a clinical epidemiologic research program started at the national Ministry of Health in this country. It mainly focused on causal identification, aimed at primary prevention of congenital anomalies. This program is now recognized as ECLAMC: Estudio Colaborativo Latinoamericano de Malformaciones Congénitas (Latin American Collaborative Study of Congenital Malformations; http://www.eclamc.org) [1].

Based on its long-term survival of almost half a century, and great impact on the international scientific literature, ECLAMC proved to be a successful experience in health research in the developing world.

More than 250 scientific publications generated from data collected by the ECLAMC program are indexed in PubMed [2]. ECLAMC constitutes an organizational innovation [3–5], applicable to other health programs in low- and middle-income countries and even to other disciplines than health. This paper was aimed to propose the essence of the ECLAMC structure hoping to initiate the design of similar programs in health sciences.

Material and Methods

The ECLAMC Program

ECLAMC is a network of professionals interested in research and prevention of birth defects. The maternity hospital network of ECLAMC examines around 200,000 consecutive births (500 g or more) per year. All major and minor anomalies diagnosed at birth are registered according to preset definitions given in a procedures manual.

Since vital and health statistics are not uniformly reported among South American countries, ECLAMC collects all the required information with a case-control method. The next nonmalformed baby of the same sex born in the same hospital is selected as a control subject for each malformed newborn. Thus, a one-to-one healthy control group matched by sex, time and place of birth is obtained.

Collected information comprises 80 variables related to genetic and environmental risk factors. The complexity of this information varies from very elementary ones, such as gender or birth weight, to more complex ones, such as prenatal exposures and very intricate information such as family history, mixed ethnicity, or parental consanguinity or nonconsanguinity.

Fig. 1. The ECLAMC hospitals network in South America. Health professionals at 211 hospitals from 12 countries have participated in the ECLAMC network from 1967 to 2012 and have registered 153,085 malformed infants in 5,282,140 consecutive births examined.

As a birth defect surveillance system, ECLAMC systematically observes the frequencies of all malformations and, in the case of an alarm for a probable epidemic of a given malformation, at a given moment, and given area, it attempts to identify its cause. Since termination of pregnancy has severe legal restrictions in South America, birth defects prevention should be concentrated on primary (preconception) and tertiary (postnatal) level interventions.

The clinician nested in an epidemiological network assures the operation of a system adding the clinical quality of the recorded data to a population sampling denominator for them.

Data handling had gone through very different systems along the almost 50 years of ECLAMC existence, from mailed paper forms to synchronized handheld devices, to current on-line interactive systems, consisting of a data entry control and storage in a set of relational MySQL databases that contains all data collected since 1967, including images (pictures, X-rays, etc.).

Although the ECLAMC Operational Manual has not been published in an available source for nonmembers of the program, it is available in Spanish and Portuguese versions upon request to the authors.

Sample

Data from all 261 hospitals from 12 countries that have participated in the ECLAMC program from 1967 to 2012 were included for network analysis (fig. 1).

Three types of data and 4 networks were evaluated in this study:

(1) Data Collection. This refers to the data income in centers (hospitals) and sending this data to the coordination. The hospitals and the coordination were considered as the 'actors' (nodes), and the quantity of sent data were the 'relationships' (links), constituting a one-mode, coordination-centered network. The analysis unit sent the information from each center to the coordination. When one hospital participated in 2 different modalities in the program (e.g. 'monitor' and 'case-control'), the units 'hospital/modality' were considered as 2 different nodes. We have evaluated 153,085 malformed infants registered from 5,282,140 consecutive births examined in 261 hospitals (315 total nodes) during the study period.

(2) Special Projects. Information was evaluated as a dichotomous variable in the matrix (1/0) according to whether or not a hospital had participated in each project to build a 2-mode network. Participation was optional, under invitation. Hospitals hav-

Poletta/Gili/Castilla

ing not participated in any of these special projects were not considered. For this network analysis, the participation of 113 hospitals in 7 projects was evaluated (120 nodes).

The 7 special research projects were:

- HIPOSP (Hypospadias): A multicultural collaborative case-control study of exogenous hormones exposure and hypospadias, also aimed at identifying positive and negative aspects of different degrees of ascertainment, recording bias and confounders [6].
- PNF (natural family planning): A study aimed to test the null hypothesis that natural family planning is not a risk factor for the occurrence of Down syndrome [7].
- DOWNSURV (Down syndrome survival): This project is a follow-up to the age of one year, to estimate mortality rates in Down syndrome cases with and without congenital heart disease, within public and private health systems [8].
- ECOTERAT (environmental teratogens): Parental economical activity and occurrence of congenital malformations in Argentina [9].
- FOLAWARE (folic acid awareness): This project examines maternal awareness on the protective role of periconceptional use of folic acid on the occurrence of congenital malformations [10].
- GLOBAL (global cleft project): A cohort study of newborns with oral clefts to evaluate the impact of systematic pediatric care on morbidity and mortality at the age of 2 years [11].
- BINS: This study intends to establish normal parameters in South American populations for the Bayley Infant Neurodevelopmental Screener (BINS) [12].

(3) Co-Authorships (Total). These co-authorships are necessary for coordinating data outcome to scientific publications involving members of each center (hospitals/coordination group) and external nodes (International Clearinghouse for Birth Defects Surveillance and Research/others). In this structural network, the links were defined between centers (nodes) as co-authorships in the same scientific paper (analysis unit); those centers with no members as authors in some publications were not considered in the network analysis. Data included 249 different publications indexed in PubMed [2] and a total of 70 nodes.

(4) Co-Authorships (Core). Nodes and links were defined in the same way as the total co-authorship network, but only the 'core' of the network was considered. The core refers to the 'key actors' of the previous network and was defined as the group of the most central nodes with the lowest total distance to all other nodes. The core group included 12 nodes and a total of 159 indexed publications.

Network Analysis

Different classical indicators were estimated to compare the structural characteristics and attributes of the ECLAMC's networks: total size (number of nodes), path count (length 1, 2 and 3), density, degree centrality, closeness centrality, and betweenness centrality. The path count is the number of links to others nodes at a length of 1, 2, and 3 consecutive paths. The density is expressed as a proportion (%) of the number of observed links to the number of total possible links among all nodes of a network [13]. Degree centrality is defined as the number of links upon a node [14]. Closeness centrality measures how 'close' a node is to other nodes in the network. Then, a central node shows lower total distance to all other nodes, and a higher closeness value [15]. Betweenness

Table 1. Attributes for 4 types of networks from the ECLAMC program

| Network attributes	ECLAMC's networks			
	data collection	special projects	co-author-ships (total)	co-author-ships (core)
Nodes (n)	315	120	70	12
Path count				
Length 1	314	226	1,112	53
Length 2	0	4,254	44,212	442
Length 3	0	15,207	1,690,961	3,264
Density (%)	0.32	3.17	46.1	80.3
Degree	243.80	0.36	3.20	11.27
Closeness	1.00	0.35	0.01	0.33
Betweenness	0	0.37	0.17	0.05

centrality quantifies the number of times a node acts as a 'bridge' between 2 other nodes and determines the relative importance of a node by measuring the fraction of paths connecting all pairs of nodes and that includes the node of interest [16].

In the present study, all these indicators were measured at a complete network-level using the 'sna' R package version 2.1 [17]. The graphic representations of the networks were made using the standard tool NetDraw version 2.134 [18].

Results

The attributes and structural characteristics of the networks from the ECLAMC data analyzed in the present study are shown in table 1 and plotted in figure 2.

The Data Collection network has a low density, a low number of paths (all of them at short distance) and a value of betweenness of zero because all peripheral nodes only interact with the coordination (the central node). This also shows clear characteristics of a centralized network with the highest value of degree and closeness of centrality (fig. 2A; table 1). In contrast, a more decentralized relationship was observed for the other 3 networks. The participation in special projects shows a more homogeneous interaction between nodes with the lowest degree of centrality and the highest value of betweenness (fig. 2B; table 1). A high interaction between nodes was observed in the co-authorships' total network, with a high number of paths and a density of 46%. This density increases to 80% and the betweenness to 0.33 when we consider the central core of this network. These 12 central
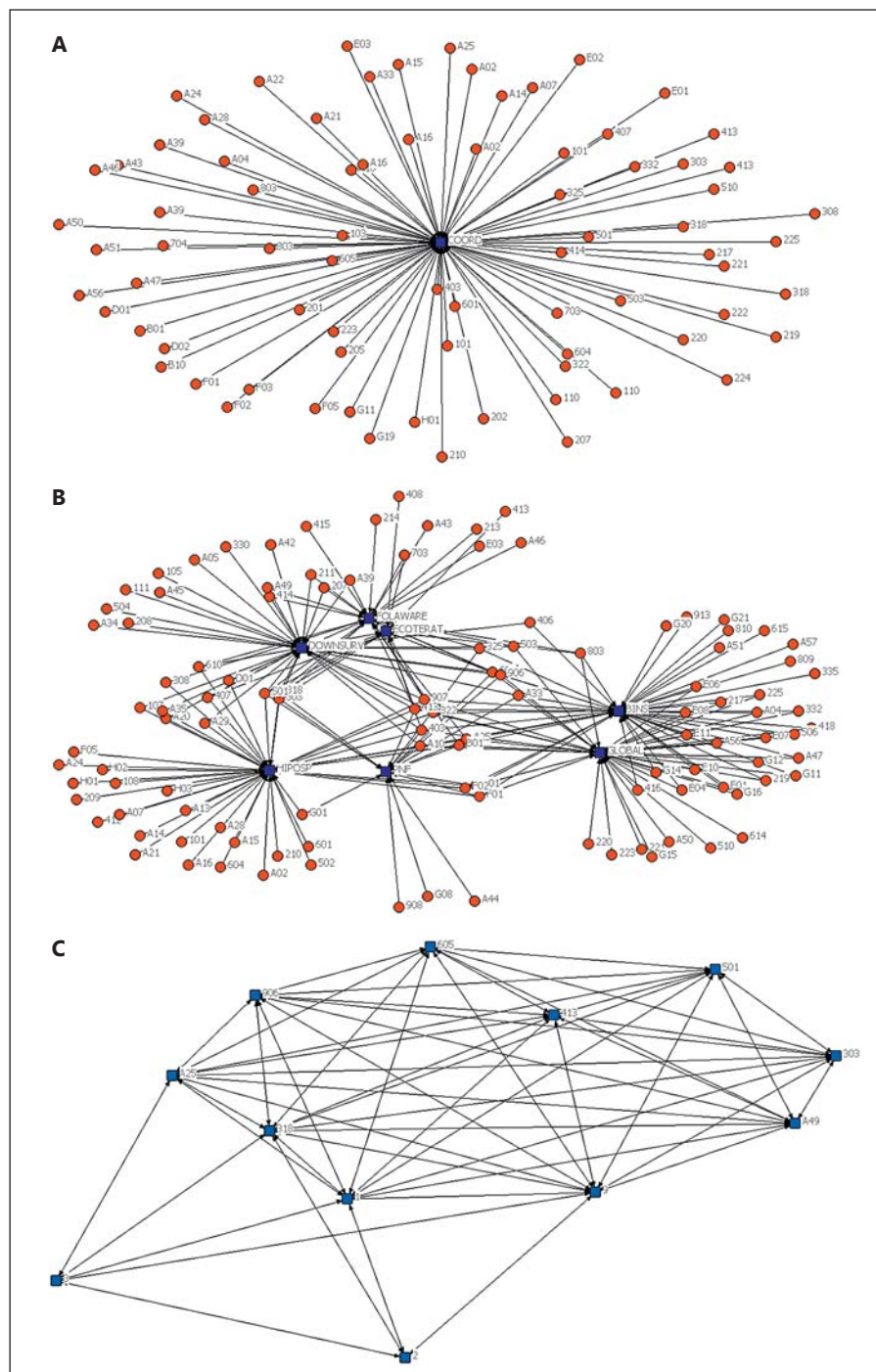
Fig. 2. Different types of relationships in the ECLAMC network. **A** Net for data income from lying-in hospitals identified by ID codes (circles) sending data for at least 500 malformed infants (Split 500) to the coordination COORD (square). **B** Net for data income from lying-in hospitals identified by ID codes (circles) participating at 7 research projects (squares): HIPOSP: Hypospadias [6], PNF: natural family planning [23], DOWNSURV: Down syndrome survival [8], ECOTERAT: environmental teratogens [9], FOLAWARE: folic acid awareness [10], GLOBAL: global cleft project [11], and BINS: BINS development testing [12]. **C** Net for data outcome to scientific publications involving 12 centers from the Core Group identified by ID codes (squares), defined actors linked to most of the other actors, while the remaining centers belong to the periphery. In this case, each participant center is an actor.

nodes could be considered as the 'key actors' of the coauthorships' network, and their collaborations in published papers represent around 60% of the total publications of ECLAMC (159 from 249 total indexed publications) (fig. 2C; table 1).

Discussion

Origin and Development

ECLAMC initiated at city level in Buenos Aires, in a few months, expanded to other cities in 3 countries and later to the rest of South America and further, involving

Poletta/Gili/Castilla

more than 200 hospitals from 12 countries of the region: Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, Paraguay, Peru, Uruguay, and Venezuela (fig. 1). During a first meeting, in 1969, a proper denomination was jointly decided for this ongoing program: ECLAMC, the Spanish acronym for Latin American Collaborative Study of Congenital Malformations.

In the second half of the 20th century, with infant mortality rates ranking at 50/1,000 or higher in Latin America, 2 main elements conditioned this new program: scarce available resources and a low priority of chronic diseases in health. The first element led to a case-control methodological approach with limited coverage; the second turned ECLAMC into a research program instead of a health program. Research funding agencies are usually more concerned with future than with current country realities (see Box 1).

During the following 20 years, 5 programs were patterned after ECLAMC: ECEMC (Spain, 1976), RYVEMCE (Mexico, 1978), RECUMAC (Cuba, 1985), CREC (Costa Rica, 1986), and REDOMAC (Dominican Republic, 1987), all of which except REDOMAC are currently active members of the International Clearinghouse for Birth Defects Surveillance and Research [19].

Lack of resources, as well as of political interest for congenital anomalies, in Latin America persisted for about half a century. Recently, however, some indications of the situation changing could be noticed in areas where infant mortality has been reduced to close to 10/1,000 births, with congenital anomalies becoming one of its leading causes. Consequently, technical assistance from ECLAMC is being requested to plan local surveillance systems for congenital anomalies in Chile, Colombia, Argentina, and Uruguay. The new systems in Chile, Colombia and Argentina are already recognized by the International Clearinghouse for Birth Defects Surveillance and Research [19], demonstrating the effective technology transfer from a research project to governmental statutory systems.

From an organizational standpoint, ECLAMC's main achievement has been its survival for 46 years, within a political and economical turmoil in Latin America, thus, proving its sustainability.

As a research program, ECLAMC's efficiency can be verified with its more than 250 publications in mainstream journals [2]. Their impact can also be measured by the available bibliometric systems, resulting in a general h-index of 38, and a g-index of 64, where 10 publications with the greatest impact were cited more than 100 times each.

Box 1. Conditions and solutions		
Local conditions		Solutions
Poor available resources	→	• Low technology: i.e. clinical epidemiology • Use of installed capacities: voluntary participation with intellectual rewarding
Low priority, political disinterest	→	• Configured for research: funding obtained from research-support agencies for specific projects using the program database • Production of high quality data: suitable for publication in mainstream journals, to reach policymakers.

ECLAMC kept updated with the ongoing development in knowledge and new technologies in the fields of: informatics, molecular biology and diagnostic, mainly image-based methods, without affecting its original research design [1]. For instance, since 1998, ECLAMC database was supplemented by a DNA biobank, and 25% of the papers published between 2000 and 2012 involved molecular data.

Network Structure

Interrelationships among all ECLAMC participants, including observational centers (maternity hospitals) and the coordinating group can be visualized as a network in the classical sociometric concept; that is, a finite set of actors and their relationships, where participating centers are the actors while their actions and events are their relationships, which can be objectively visualized free of preconceived premises [20].

For each one of their activities, the ECLAMC adopted and adapted different structures that can be defined, from the social network analysis point of view, as a centralized, unimodal and afferent network for data collection (fig. 2A); as a decentralized, bimodal and interactive network for special projects (fig. 2B); and co-authorship of published papers (fig. 2C).

The large experience of the ECLAMC program can be outlined to facilitate its transfer to future programs, projects and studies, mainly, but not exclusively centered on chronic, nontransmissible diseases located in low- and middle-income areas. Eight identified key elements are

briefly presented in Box 2, as the whole structure of ECLAMC has already been published elsewhere [1].

In spite of ECLAMC being a nonhierarchial organization in its relationship between the coordinating group and the participating centers, the research protocol, or Operational Manual, is the 'canon' for the whole program, and its working definitions are to be respected. This procedures manual was created and updated through open discussions and decisions by all participants in 44 annual meetings that took place uninterruptedly, and this collaborative group authorship justifies its mandatory reinforcement.

South by North

One clear pitfall of the proposed organization is the delay in the process to convert knowledge into action because information produced by a research, noninstitutional program does not have a direct impact on health programming. The usual steps followed in this process include information production, publication in prestige journals, their acceptance by American and/or European health agencies, and finally, health action in the countries where the information was generated.

ECLAMC experienced such delays in South America with the prevention of spina bifida by folic acid food fortification [21], of oculo-cardiac anomalies by rubella vaccination [22] and of thalidomide embryopathy which continues to occur far into the 21st century [23].

Conclusions

The transferable elements from the ECLAMC program include the collaboration between motivated expert people, voluntarily accepting the same research protocol, with a sense of belonging to the working-group, based on mutual trustfulness within a transparent framework, with explicit rules, and aimed at producing data of internationally competitive quality. This model is proposed for future health programs, mainly in low- and middle-income areas.

Acknowledgements

References

1 Castilla EE, Orioli IM: ECLAMC: The Latin-American collaborative study of congenital malformations. Community Genet 2004;7:76–94.
2 PubMed/MEDLINE: http://www.ncbi.nlm.nih.gov/pubmed/?term=ECLAMC[All+Fields]+OR+%28Castilla+EE[Author]+OR+Orioli+IM[Author]+OR+Lopez+Camelo+JS[Author]+OR+Lopez-Camelo+J[Author]+OR+Dutra+MG[Author]+OR+Dutra+GM[Author]%29 (accessed September 18, 2013).
3 Snyder-Halpern R: Indicators of organizational readiness for clinical information technology/systems innovation: a delphi study. Int J Med Inform 2001;63:179–204.
4 Ensor T, Ronoh J: Impact of organizational change on the delivery of reproductive services: a review of the literature. Int J Health Plann Manage 2005;20:209–225.
5 Lukas CVD, Holmes SK, Cohen AB, Restuccia J, Cramer IE, Shwartz M, Charns MP: Transformational change in health care systems: an organizational model. Health Care Manage Rev 2007;32:309.
6 Källén B, Castilla EE, Robert E, Lancaster PA, Kringelbach M, Mutchinick O, Martínez-Frias ML, Mastroiacovo P: An international case-control study on hypospadias. The problem with variability and the beauty of diversity. Eur J Epidemiol 1992;8:256–263.
7 Castilla E, Lopez-Camelo J, da Graça Dutra M, Queenan J, Simpson J: The frequency and spectrum of congenital anomalies in natural family planning users in South America: no increase in a case-control study. NFP-ECLAMC Group. Natural Family Planning. Latin-American Collaborative Study of Congenital Malformations. Adv Contracept 1997;13:395–404.
8 Castilla EE, Rittler M, Dutra MG, Lopez-Camelo JS, Campaña H, Paz JE, Orioli IM: Survival of children with Down syndrome in South America. ECLAMC-Downsurv Group. Latin American Collaborative Study of Congenital Malformations. Am J Med Genet 1998;79:108–111.

9   Castilla EE, Campaña H, Camelo JS: Economic activity and congenital anomalies: an ecologic study in Argentina. ECLAMC ECO-TERAT Group. Environ Health Perspect 2000;108:193–197.
10 Castilla EE, da Graça Dutra M, Lopez-Camelo JS, Rittler M, Orioli IM: Awareness of the benefit of periconceptional folic acid supplementation in South America. Community Genet 2000;3:71–76.
11 Rittler M, Cosentino V, Lopez-Camelo JS, Murray JC, Wehby G, Castilla EE: Associated anomalies among infants with oral clefts at birth and during a 1-year follow-up. Am J Med Genet A 2011;155A:1588–1596.
12 McCarthy AM, Wehby GL, Barron S, Aylward GP, Castilla EE, Javois LC, Goco N, Murray JC: Application of neurodevelopmental screening to a sample of South American infants: the Bayley Infant Neurodevelopmental Screener (BINS). Infant Behav Dev 2012;35:280–294.

13 Sabidussi G: The centrality index of a graph. Psychometrika 1966;31:581–603.
14 Freeman LC: Centrality in social networks conceptual clarification. Soc Networks 1979; 1:215–239.
15 Newman ME: A measure of betweenness centrality based on random walks. Soc Networks 2005;27:39–54.
16 Freeman LC: A set of measures of centrality based on betweenness. Sociometry 1977;40: 35–41.
17 Butts CT: Sna: tools for social network analysis: R package version 21. 2010. http://cran.r-project.org/web/packages/sna/sna.pdf.
18 Borgatti S: Netdraw software for network visualization. Lexington, Analytic Technologies, 2002.
19 ICBDSR: International Clearinghouse for Birth Defects Surveillance and Research. Annual report 2011, with data for 2009. Rome, ICBDSR, 2011.

20 Wasserman S, Faust K: Social Network Analysis: Methods and Applications (Structural Analysis in the Social Sciences). Cambridge, University Press, 1994.
21 Lopez-Camelo JS, Castilla EE, Orioli IM; INAGEMP (Instituto Nacional de Genética Médica Populacional); ECLAMC (Estudio Colaborativo Latino Americano de Malformaciones Congénitas): Folic acid flour fortification: impact on the frequencies of 52 congenital anomaly types in three South American countries. Am J Med Genet A 2010; 152A:2444–2458.
22 Orioli IM, Camelo JSL, Rittler M, Castilla EE: Sentinel phenotype for rubella embryopathy: time-space distribution in Brazil. Cadernos de Saúde Pública 2011;27:1961–1968.
23 Schuler-Faccini L, Soares RC, de Sousa AC, Maximino C, Luna E, Schwartz IV, Waldman C, Castilla EE: New cases of thalidomide embryopathy in Brazil. Birth Defects Res A Clin Mol Teratol 2007;79:671–672.