

Haemophilia in the developing world: successes, frustrations and opportunities

M. TEZANOS PINTO* and Z. ORTIZ†

**Instituto de Hematología, Academia Nacional de Medicina, Buenos Aires, Argentina; and* †*Centro de Investigaciones Epidemiológicas, Academia Nacional de Medicina, Buenos Aires, Argentina*

Summary. There is a need to bridge key gaps between high- and low-income countries and individuals; between health policy and clinical practice; and between producers and users of healthcare technology and scientific evidence. The objective of this report was to perform a diagnosis of the situation in the developing world through a survey. This survey was conducted to gather specific information on various aspects related to haemophilia. Countries were chosen by their comparability in infant and adult mortality rates according to the regionalization proposed by the World Health Organization. These indicators are very sensitive to socioeconomic conditions, and have been widely used to study health inequalities. All regions, except Africa and the East Mediterranean, were represented. Africa was excluded because its indicators were not comparable. The East Mediterranean was not represented because of difficulties in contacting investigators. Twenty-one country representatives

were contacted, and 11 answered the questionnaire. Successes obtained by developing countries are based more on the skills and creativity of the local professionals than on the availability of state-of-the-art technology. Frustrations were related to disease underregistration and the limited availability of treatment products. Haemophilia care in the developing world is not as fair as we would like it to be. Governments do not always cover treatment costs, and a very small percentage of the national health budgets is allotted to haemophilia care. The role of the World Federation of Hemophilia was considered crucial by all the investigators surveyed. Training programmes and supply of factor concentrates were the main contributions identified by the respondents.

Keywords: developing world, frustrations, haemophilia care, inequalities, successes survey

Introduction

Spectacular progress has been made over the past quarter-century in the diagnosis, treatment, rehabilitation, social integration and education of people with haemophilia. We are all aware of the commitment and efforts undertaken by numerous researchers to develop a gene therapy aimed at curing the disease, or, at least, at changing the phenotype of patients with severe haemophilia to moderate or mild. Regardless of the fact that our generation may or may not see these developments come true, these are unarguably the goals.

However, while we observe these developments with great interest, we also see how the social

dimension of globalization retreats. According to the latest estimates of the International Labour Organization, over the past decade there has been an increase in the declared unemployment worldwide and an increase in poverty within the developing world. Unemployment rates have increased since 1990 in Latin America, the Caribbean and southeast Asia, and since 1995 in East Asia [1] (Fig. 1). In Latin America and the Caribbean, 15% of the population lives in extreme poverty (income of <US\$1 per day, according to the United Nations indicator) [2]. In terms of growth, only 16 developing nations grew more than 3% per year between 1985 and 2000. In contrast, 55 developing countries grew <2% yearly, and of these, 23 had negative growth.

Socioeconomic situation is a determining factor in health. Evidence shows that the relationship between poverty and health is clear, direct and unquestionable [3]. Whenever we examine rates related to mortality, morbidity or self-perception of health, the

Correspondence: Instituto de Hematología, Academia Nacional de Medicina, Pacheco de Melo 3081, CP 1425, Buenos Aires, Argentina.
Tel.: + 54 11 4805 6890; fax: + 54 11 4806 6638;
e-mail: mtezanos@hematologia.anm.edu.ar

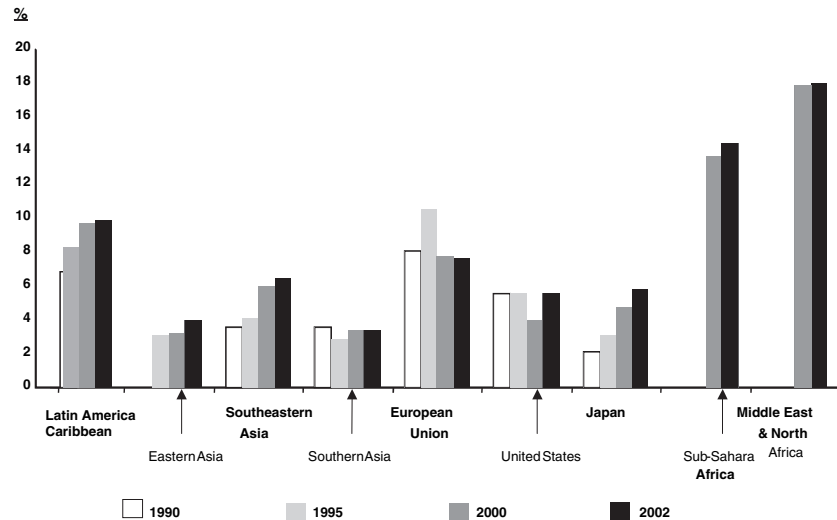


Fig. 1. Open unemployment rates for various regions of the world, 1990–2002 (in percentages).

result is always the same: those groups of people who are worst off in economic, social and educational terms are also the ones who are in the worst health situation.

Inequalities in haemophilia

These striking differences in growth and social conditions are giving rise to a new economic geography that will, no doubt, have an ever-growing impact on haemophilia. Two major issues should be addressed: diagnosis and treatment.

International organizations estimate there are half a million people with haemophilia worldwide. Prevalence rates are from 105 to 160 per million of the male population, of whom fewer than one-third are diagnosed. In Australia, the USA and other developed countries, 90% of the patients are diagnosed, whereas some developing countries have records of only 5% of their patients, or no registries whatsoever.

Bridging the gaps

It will not be an easy task to alter social inequalities in international healthcare, both because of differing national structural characteristics and socioeconomic difficulties. The acknowledgement of successes, frustrations, and opportunities in haemophilia in the developing world may help to bridge some of the key gaps that have been identified: between high and low-income countries and individuals; between health policy and clinical practice; and between producers and users of healthcare technology and scientific evidence.

The objective of this report was to perform a diagnosis of the situation through a survey that included 20 semistructured questions and an open question for gathering additional information. This survey was conducted to gather specific information on various aspects related to haemophilia (Table 1).

Countries were chosen for their comparability in infant and adult mortality rates according to the regionalization proposed by the World Health Organization [4]. These indicators are very sensitive to socioeconomic conditions, and have been widely used to study health inequalities.

All regions, except Africa and the East Mediterranean, were represented. Africa was excluded because its indicators were not comparable: all countries in the region have high infant mortality rates. The East Mediterranean is not represented because of difficulties in contacting investigators. Twenty-one country representatives were contacted, and 11 answered the questionnaire.

Survey results

Almost all survey responders were able to state the registered number of patients with haemophilia and the estimated number of people with haemophilia in their countries. The difference between both numbers seems to indicate a significant under-registration of the disease in these nations. The availability of treatment products is heterogeneous, but most countries did not have the full array of treatments available in developed countries. According to the results of the survey, haemophilia care in the developing world is not as fair as we would like it to be. Governments do not always cover treatment

Table 1. Aspects covered by the questionnaire

Aspect	Data
Population statistics and disease magnitude	Population Estimated number of PWH Number of registered PWH Median age
Availability of treatment products	FFP Cryoprecipitate Factor VIII and factor IX concentrates Inhibitors FEIBA Factor VIIa Use of factors: units per year
Haemophilia care system	Number of patients that receive treatment on a regular basis Who pays the medical care and treatment Inhibitors tested on a regular basis Assessment of the progress in haemophilia care Short-term perspective for haemophilia care in each country
Healthcare system	% of the national budget allotted to health % of the health budget allotted to haemophilia % of PWH who have access to multidisciplinary care
Sociopolitical	The role of the WFH Social integration of PWH
Additional information	Comments

PWH, people with haemophilia; FEIBA, factor VIII bypassing activity.

costs, and a very small percentage of the national health budgets is allotted to haemophilia care.

Finally, the role of the World Federation of Hemophilia (WFH) was deemed crucial by all the investigators surveyed, particularly for its work in training professionals and in supplying factor concentrates.

Key success factors

Some people believe that Science is a luxury that can only be afforded by large, wealthy countries, which spend money on it because they are rich. This is a serious mistake. Large, wealthy nations spend money on science because science is a great business and a way of becoming rich...That is why, as Nehru used to say, underdeveloped countries cannot afford not to engage in Science and Technology.

*Bernardo A. Houssay, Argentina (1887–1971)
Winner of the Nobel Prize for Medicine, 1947*

Despite the distance that separates the developing and developed world, we cannot ignore the successes

obtained by developing countries, which are based more on the skills and creativity of the local professionals than on the availability of state-of-the-art technology. We have had ample proof of this throughout the history of haemophilia breakthroughs. In 1947, Pavlovsky *et al.* in Buenos Aires, Argentina, observed the mutual correction in clotting when plasmas from haemophilia patients with similar clinical conditions and therapeutic requirements were mixed. Pavlovsky explained his findings, although he may not have understood the full implications. Five years later, in 1952, Aggeler *et al.* in San Francisco, Macfarlane *et al.* in Oxford and Shulman and Smith in New York described a disease that was genetically similar to haemophilia but was brought about by a different defect that had not been previously reported as a coagulation factor: factor (F) IX, the cause of haemophilia B.

In 1959, Simonetti *et al.* [5], also in Argentina, managed to eliminate 80–90% of fibrinogen by adding tannin to the I-O fraction. Although better methods were later developed by industry, Simonetti's method enabled preparation of a concentrate that offered good stability and was well-tolerated. This method was used in clinical practice throughout the 1960s.

After Ahlberg's initial description in 1971 regarding the use of colloidal ^{198}Au for the treatment of chronic synovitis, several Latin American researchers published their experiences, reporting satisfactory responses in over 80% of the patients treated with ^{198}Au , ^{186}Re , and ^{90}Y . The method employed was severely questioned by the international medical community owing to the biological risk posed by the radiation, particularly by ^{198}Au , which emits gamma rays. However, Fernandez Palazzi *et al.* [6], undertook a planned study at the Institute of Haematology in Buenos Aires, and demonstrated that the chromosomal alterations attributed to the radioactive material were not premalignant and were no longer present a few years later.

Another pathology, almost unheard of in the developed world but still observable in emerging countries, is the haemophilic pseudotumour, which required extensive surgery with uncertain results as the only therapy until Fernández Palazzi in Caracas, Venezuela [7], described a percutaneous treatment. This technique was subsequently adopted by other professionals, and has avoided many amputations.

Achievements made by institutions or state agencies that benefit all patients have a greater importance. In the Czech Republic, all patients were treated with cryoprecipitates until 1990 [8]. Since then, patients have been treated solely with factor

concentrates prepared from Czech plasma. Blood is obtained by the blood-transfusion service and fractionated by international companies. Home treatment was initiated in 1994 for patients with severe disease and has since been made available to patients with moderate haemophilia. In these programmes, consumption per patient per year is 30 000–80 000 U of FVIII or FIX, and annual consumption doubled from 9000 to 18 000 U per patient per year in 1998, representing 1.2 units per inhabitant.

In Thailand, the main success has been the impulse given to the National Blood Transfusion Service and the decision to collect plasma only from unpaid donors [9]. The Queen is involved in this campaign through the Thai Red Cross Society, which rewards individuals each time they reach their seventh donation at the Transfusion Services. The ceremony, presided over by the Queen herself or by some other member of the royal family, is appreciated and deemed a great honour. The example set by the National Organization has extended to non-governmental agencies and even to private undertakings.

In Brazil, in the 1990s, the Health Ministry became involved in a programme that was perfected years later and aims at achieving a fair distribution of factor concentrates until an allotment of 20 000 U per patient per year is reached. This is enabled by the expansion of regional and coordination blood centres represented in each of the 26 provinces [10]. It is likely that, in the near future, we will need to include China as an example of development brought about by a spectacular change in the political and economic regime. A promising change is already being perceived at the Tianjin Haemophilia Centre [11].

Some frustrations

Fairness in the way of paying for health assistance and the capacity of the systems to meet individuals' expectations with regard to their treatment are just two of the goals that health systems should pursue. Very little is being achieved in these areas. In the poorest countries of the world, the greater part of the population, particularly the impoverished, must pay their own health expenses. The resources allotted to health systems are distributed very unequally, and are not in keeping with the health problems faced by the population. Low- and middle-income countries represent just 18% of the global income, and 11% of worldwide health expenses (4% of those countries' GNP), yet 84% of the world population inhabit these countries and bear 93% of the global morbidity [4].

Haemophilia is a low-incidence, high-cost disease that has a potentially catastrophic outcome; it meets all the necessary criteria for public funding to be used in the administering and financing of treatment that has proven to be beneficial (Fig. 2), but funding is determined by how priorities are set, and there are no clear criteria for this; our results in this area show great variations. In our opinion, this is the most significant frustration. We must all work closely together to alter this situation.

Survey

In this survey, we specifically inquired about the role the WFH plays in developing countries, and which should be the objectives for the near future. The responders to the survey unanimously pointed out the remarkable efforts undertaken by the WFH to

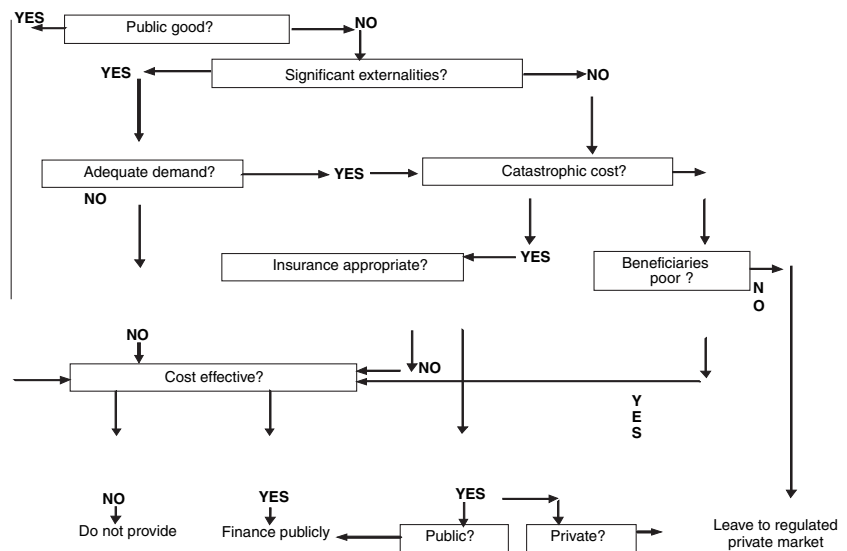


Fig. 2. Questions to ask in deciding what interventions to finance and provide. Adapted from Musgrove P. Public spending on healthcare: how are different criteria related?. *Health Policy* 1999; 47:207–33.

approach emerging countries, offering different options and contributing ideas and solutions for current and future problems.

International Haemophilia Training Centers Program

This programme, approved by the WFH in Moscow in 1969 and implemented in 1973, enables professionals working in various fields of haemophilia care in developing countries to visit experienced, quality centres in developed countries for short (1–2-month) stays. At present, there are 31 international haemophilia treatment centres (IHTCs). The selection of nominees is approved by the IHTC Committee, which then chooses the centre that offers the greatest advantages as to geographical proximity and cultural and language affinities. Along the years, the IHTC directors have observed many major advantages as well as some issues that should be addressed.

The Twinning Program

Devised by Mariani [12], this programme was approved in 1993 and is the single most significant contribution for emerging countries. This report is not meant to provide a detailed description of the objectives or the methodology used by each centre, but to highlight the successes that are permanently observed. It is very gratifying to observe centres that were once the emerging twin performing as the established twin in a new twinning partnership. It should also be highlighted that those centres that took on the role of established twin acknowledge also having benefited from the partnership; teaching is the best way of learning.

The journal, Haemophilia

As Lee points out [13], the distribution of this journal should be more widespread in the developing world. Despite all the advances in communications that allow readers to access articles via Internet, 92% of the subscribers are from the UK, USA and Europe.

Regional workshops

The WFH has organized workshops designed to help those in charge of dealing with regulatory issues on plasma and blood products to face the changes. One workshop was held in Miami, USA in 2002 for Latin America, and another in Budapest, Hungary, for

representatives from 14 Central and Eastern Europe countries.

The WFH is striving to foster the emergence of new leaders in haemophilia organizations from developing countries, and to bolster these organizations. Accordingly, the First Regional Workshop for Skills Development for Latin American Haemophilia Organizations was held in Panama in 2003. Fifty-nine participants from 19 countries attended the meeting. A particularity of this workshop was that the facilitators of the various courses were leaders and/or professionals from those countries. A similar workshop, attended by 45 participants from 27 countries, was held in Murcia, Spain in 1999.

In order to set priorities realistically, a great deal of information is required, especially epidemiological data [14]. The Annual Global Survey, an excellent WFH initiative, and our study are experiences that help us make a diagnosis of the different realities of each country. They no doubt contribute to a better understanding of what is going on in haemophilia. Nevertheless, in order to have an accurate awareness of all the aspects related to haemophilia, it would be necessary to establish universal registries that should be implemented in all member countries of the WFH; totally unbiased information could thus be obtained.

Conclusions

With regard to the IHTC Programme, it is essential that the WFH control, or at least be aware of, the development of the professionals trained at IHTCs and their commitment to continue working in and for haemophilia. The implementation of a continuing medical education programme in which fellows must agree to read related articles, chosen by the WFH, and answer a questionnaire prepared by the IHTC Committee, could provide a means for keeping fellows active and updated in their fields of interest. This idea might be further enhanced by granting a certificate of approval that would constitute evidence of the fellows' knowledge, with periodic re-certification.

The developing world is still in the throes of deep educational, economic, and even political crises. Without doubt, we will witness a slow but steady development as prevailing conditions improve. These are the perspectives of a hopeful tomorrow, for at present the care of people with haemophilia in these restricted economies differs substantially from that provided in stronger economies. Replacement therapy is not easy to provide, and this fact impacts sharply on the life expectancy and quality of life. Optimum survival rates are associated with replace-

ment therapy of at least 1 U per inhabitant; however, data from the WFH Global Survey 2002 shows that consumption of FVIII concentrates varies from over 3 U per inhabitant in Germany, Australia and the USA to 0.01 U per inhabitant in India and Indonesia. Meanwhile, the WFH does everything within its means, and whenever possible and necessary, provides anti-haemophilic concentrates for the care of patients throughout the world. It would be very satisfying if these efforts were transferred to governments, and if the industrialized world would look upon the developing countries as friends and lift the commercial trade barriers that so greatly hamper the producers of primary goods.

Achievement of the sustainable, long-term benefits of reducing health inequalities requires the integration of a comprehensive range of policies into mainstream policy and planning.

Acknowledgements

We wish to thank Karine Frisou of the World Federation of Hemophilia; Hector Beccar Varela of the Fundación de la Hemofilia in Argentina; Silvia Tenconi, Silvia Sempé and Virginia Viegas of the Academia Nacional de Medicina – Buenos Aires for their help in the preparation of this manuscript; Olga Suárez for her help with the charts; and especially Mónica Cabouli for her insightful review and suggestions. We also wish to thank our colleagues who kindly answered our survey: Diana Careri, Argentina, Renchi Yang, China, Lee Dae-Geun, Korea Republic, Martha Monteros, México, Bélgica Moreno, Panama, Yuri Zhulyov, Russia, Angelika Batorova Head, Slovakia, Partraporn Isarangkura, Thailand, Bulent Zulfikar, Turkey, Alicia Pereira and Douglas Piquinela, Uruguay, Norma de Bosch, Venezuela.

References

- 1 Comisión Mundial sobre la Dimensión Social de la Globalización. *Por Una Globalización Justa. Crear*

- Oportunidades para Todos*. February 2004. Available at: <http://ilo.org/public/english/wcsdg/docs/report.pdf>.
- 2 United Nations. *United Nations Millennium Development: Goals, Data and Trends, 2002*. Report of the Inter-Agency Expert Group on MDG Indicators, New York, April 2002. Available at: http://millenniumindicators.un.org/unsd/mi/mdg_report.pdf.
- 3 Evans RG, Barer M. L, Marmor TR, eds. *Why Are Some People Healthy and Others Not? The Determinants of Health of Populations*. New York: Aldine de Gruyter, 1994.
- 4 Organización Mundial de la Salud. *Listado De Estados Miembro Según la Región de la Oms y los Estratos de Mortalidad. En Informe Sobre Salud en El Mundo 2000, 2000. Mejorar El Desempeño de los Sistemas de Salud*. Suiza: Ginebra. 2000; 228–30.
- 5 Simonetti C, Casillas G, Pavlovsky A. Purification du facteur VIII antihémophilique (FAH). *Hemostase* 1961; 1: 57.
- 6 Fernández Palazzi F, Caviglia H. On the safety of synoviorthesis in haemophilia. *Haemophilia* 2001; 7 (Suppl. 2): 50–3.
- 7 Fernández Palazzi F, Rivas S, Bosch N *et al*. Percutaneous treatment of haemophilic cysts and pseudotumors. In: Lusher JM, Kessler CM, eds. *Hemophilia and von Willebrand's Disease in 1990*. Amsterdam: Excerpta Medica 1991; 157–64.
- 8 Vorlova Z, Matyskova M, Hrachovinova I *et al*. Haemophilia care in the Czech Republic. *Haemophilia* 2000; 6: 431–8.
- 9 Isarangkura P. Haemophilia care in the developing world. Benchmarking for excellence. *Haemophilia* 2002; 8: 205–10.
- 10 Antunes SV. Haemophilia in the developing world. The Brazilian experience. *Haemophilia* 2002; 8: 109–202.
- 11 Zhang L *et al*. Retrospective analysis of 1312 patients with haemophilia and related disorders in a single Chinese Institute. *Haemophilia* 2003; 9: 696–702.
- 12 Mariani G. The Haemophilia Centre Twinning Programme. *Haemophilia* 1996; 2: 125–7.
- 13 Lee CA. World Federation of Haemophilia developing world programmes. *Haemophilia* 1988; 4 (Suppl. 2): 59–63.
- 14 O'Mahony B. *Global Haemophilia care. Challenge and Opportunities*. World Federation of Haemophilia, 2002. Available at: <http://www.wfh.org>.