Accepted: 30 December 2017

DOI: 10.1111/hae.13409

ORIGINAL ARTICLE

Clinical haemophilia

WILEY Haemophilia

First-year results of an expanded humanitarian aid programme for haemophilia in resource-constrained countries

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Introduction: The gaps in haemophilia treatment around the world are enormous; approximately 60% of an estimated 475 000 individuals are not identified. Of the 187 000 diagnosed, 30% (57 000) access clotting factor replacement therapy. Since 1996, humanitarian aid distributed by the World Federation of Hemophilia (WFH) has played a minor, yet vital role providing life-saving clotting factor to countries in emergency situations. Donated amounts have been small and sporadic, often salvaging short-dated products, providing little opportunity to leverage donations with governments. In 2015, a prospective donation programme of 100 million I.U. per year of extended half-life factor VIII and IX over 10 years was established, necessitating the development of new logistics and training programmes by WFH.

Aim: To measure the impact of a greatly expanded haemophilia humanitarian aid program.

Materials and methods: In 2016, the first full year of the expanded programme, WFH, distributed products to 58 countries with factor VIII usage <1 I.U. per capita, a level incompatible with long-term survival and far below the 4 I.U. FVIII per capita minimum established in Europe.

Results: The scope of the programme and utilization data for 2016 indicate primarily use for acute bleeding, orthopaedic and emergency surgeries. Compared to 2014, 2016 data showed substantial increases in patients served (5.9-fold, from 2119 to 14 579), surgeries performed (37-fold) and bleeds treated (6.9-fold). Patients on prophylaxis rose from 0 to 852, including 458 children under 10 years old.

Discussion: The expanded humanitarian aid programme impacts an estimated 10% of individuals with haemophilia previously unable to access treatment.

Conclusion: This programme represents an unprecedented public-private partnership to deliver medicines to individuals with no access. Further, the programme offers the prospective opportunity to engage governments to take more responsiblity for increasing training, medical management, and product supply in 58 resource constrained countries.

KEYWORDS

clotting factor, donation, Factor VIII, haemophilia, haemophilic arthropathy, humanitarian aid, public-private partnership

1 | INTRODUCTION

Severe haemophilia (factors VIII or IX <1%) is a lethal disease left untreated. Life expectancies in Western Europe and North America have gradually increased from approximately 20 years in the 1950s[1] to approaching normal today,[2-4] due primarily to widespread availability of clotting factors VIII and IX replacement therapies. Early diagnosis and the introduction of primary prophylaxis have dramatically improved the lives of individuals with haemophilia. Thus, a near normal life expectancy is feasible in countries where reimbursement systems cover the cost for prophylaxis treatment.

This is not the case in resource-constrained countries, which comprise 70% of the world's population, and by extension, up to 70% of the world's individuals with haemophilia, leaving the majority undiagnosed with high morbidity and mortality due to uncontrolled bleeding.[5-8] In lower income countries, based upon World Bank economic ratings, less than 10% of the patients have been identified.[9] Of those diagnosed globally, only 30% have access to clotting factor, resulting in a short life expectancy of 70% of the identified patients and presumed substantial mortality among those not identified.[6-8]

The World Federation of Hemophilia (WFH) provides training programmes for healthcare providers and persons with haemophilia on the comprehensive care model for haemophilia and for the development of advocacy skills. It has been challenging to obtain government commitments to fund Haemophilia Treatment Centers (HTC) and purchase lower cost clotting factors. The provision of small donations of clotting factor to individual countries has often not been sufficient impetus to convince governments to support haemophilia programmes and even basic on-demand therapy for life-threatening bleeds.

The WFH currently represents 134 national member patient organizations (NMOs) worldwide. An annual global survey is conducted to assess the amount of clotting factor utilized as a function of the total population (per capita).[9] This approach to quantify intracountry usage assumes a similar global incidence of haemophilia. Through this process, an estimate for I.U. of clotting factor required from basic survival to full prophylaxis can be estimated.[7]

In resource-rich countries, prophylactic use of factor VIII in children and adults is the standard of care[10,11] and clotting factor concentrates (CFC) up to ~10 I.U. per capita are now available.[9] In contrast, in resource-constrained countries which WFH targets for humanitarian aid, per capita use is often well below 1 I.U. per capita, a disparity directly responsible for the observed high mortality.[7] The recent European Directorate for Quality of Medicine (EDQM) recommendation calls for minimum 4 I.U. per capita] to provide a prophylaxis strategy to minimize arthropathy.[12] We present the first full-year results of the expanded WFH Humanitarian Aid Programme (HAP) in 58 countries consuming <1 I.U. per capita in clotting factor.

2 | HUMANITARIAN AID PROGRAMME MATERIALS AND METHODS

2.1 | Goals of the programme

Goals were established and include 1, Reach the majority of qualified countries (<1 I.U. per capita) and treat as many persons with haemophilia (PWH) as possible within each country; 2, Increase case finding and local government engagement; 3, Give healthcare providers (HCPs) the opportunity to develop multiple skills in management and logistics of PWH; 4, Promote low-dose prophylaxis for children under 4 years of age; 5, Decrease as much as possible mortality and improve quality of life.

2.2 | Selection criteria

Countries were selected on the basis of the Annual Global Survey of clotting factor usage of <1 I.U./capita[9] and knowledge of the state of the HTC and NMO within a country. Countries selected must have the ability to diagnose and distinguish between haemophilia A and B, and perform a quantitative or qualitative assay for inhibitor (neutralizing antibodies) detection. Product donors are not involved in country selection, and donations go to countries which import little to no product.

2.3 | Logistics

Based on an approved distribution plan, the manufacturer ships product as needed to the distribution facilities, where a range of vial sizes are stored. A single HTC or the NMO, or the Ministry of Health, is designated as the recipient of the donations. From the single point of storage within a country, product may be shipped to other HTCs within the country under the responsibility of the main centre in each country. For quantities ≥1 million I.U. per country per year, audits and inspections are carried out by WFH to ensure chain of custody and lockable cold storage rooms.

2.4 | Training

WFH training materials were prepared for the expanded programme, including factsheets on storage and handling, administration and dosage, disposal of material, inhibitor detection, low-dose prophylaxis, monitoring for adverse events and product recall instructions. These factsheets are supplemented by frequent telephone and email contact and periodic regional and in-country visits. In the visits, training is generally conducted over 2 days by WFH staff and volunteers and includes didactic information on managing haemophilia as well as case reports and case series from recipient physicians on how the product has been utilized.

2.5 | Key performance indicators

An online reporting system was developed to identify the actual product needs in real time and to provide product utilization metrics in each country. A series of Key Performance Indicators (KPI) were identified to reflect the degree of success in product utilization and the purpose for which product was used in patients. Dosing and usage of products is the responsibility of the treating physician, and no individual patient outcome data are collected. Thus, ethics committee approvals were not needed.

3 | RESULTS

Since 1996, the WFH Humanitarian Aid Programme has conducted humanitarian aid operations in 90 countries, cumulatively distributing 322 million I.U. of clotting factor through 2014 (Figure 1). Donations were unpredictable, facilitating life-saving interventions but not sustainable on-demand treatment of bleeding episodes. From 2009, CSL Behring started prospectively providing 2-3.3 million I.U. per year of clotting factor, followed by Grifols in 2014 donating 20-30 million I.U. per year, and others, allowing some multiyear strategic targeting of donations to support infrastructure development within a few countries (Table 1). By 2014, multiyear agreements were signed with several manufacturers and plasma collection agencies for prospective, multiyear donations. These donations were used primarily for emergency situations and were not sufficient for routine on-demand therapy, non-emergent orthopaedic reconstructive surgeries or prophylactic regimens. The majority of the major manufacturers do not contribute to a prospective humanitarian aid programme, despite owning the majority of the worldwide market.

In 2014, two companies, Bioverativ (formerly Biogen) and Sobi, announced a contribution of 1 billion I.U. of extended half-life (EHL) clotting factor to the worldwide bleeding disorders community over 10 years (Table 1). Of this, the WFH agreed to distribute ~100 million I.U. per year over 5 years. The programme began in mid-2015, and in 2016, the first full year of the expanded WFH HAP 144 million units of all products, including 114 million units of EHL products, were distributed to 58 countries (Figure 2). The approximate percentage of PWH

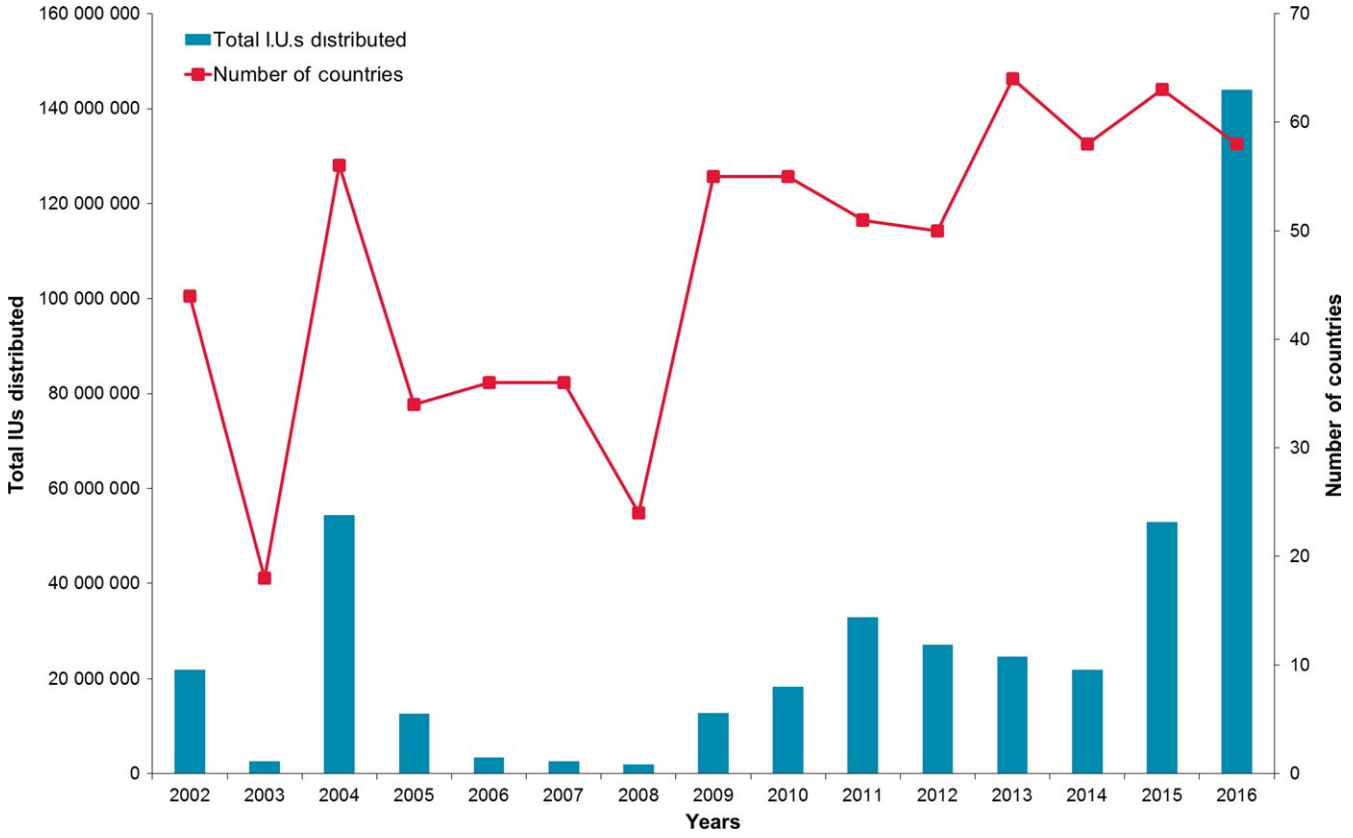

FIGURE 1 Humanitarian aid donations 2002-2016 [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Prospective Clotting factor donations to WFH

Supplier	Number of units/year (MIUs)	Years of donation (inclusive)
Bioverativ-SOBI*	100	2015-2020
Green Cross	2	2017-2019
CSL Behring	2-4	2010-2018
Grifols	20-30	2014-2021
Project Recovery (Biotest and Canadian Blood Services)	3	2014-2017

*Bioverativ was spun off from Biogen in January 2017. MIU, Millions of I.U.s

reached, relative to the total number identified in a country, is listed in Figure 2.

To establish the countries most in need of aid, data from the annual global survey were utilized.[9] This approach to quantify intracountry usage assumes a similar global incidence of haemophilia; thus, differences in prevalence based upon early death and lack of patient identification do not impact the results. Through this process, an estimate for I.U. of clotting factor required for basic survival to full prophylaxis can be estimated.[7]

In 2015-16, 8 regional humanitarian aid trainings were conducted in host countries for 335 physicians from the majority of the 58 donation countries. Educational topics include historical and current treatment practices, inhibitor (neutralizing antibody) diagnosis and treatment, musculoskeletal complications, dosing of conventional and extended half-life products and presentations from individual countries on their haemophilia care situations and reports on their difficult cases. Specific review of laboratory assays for FVIII and FIX as well as methods of inhibitor detection was also conducted.

A series of KPIs were established to quantify the impact of the expanded WFH HAP programme (Table 2). The WFH HAP programme has seen marked changes between 2014, when about 21 million I.U. were donated, and 2016, the first-year donations exceeded 100 million I.U. Surgeries rose from 21 in 2014-675 in 2016. The number of countries performing surgery rose from 3 to 22. Patients on prophylaxis rose from 0 to 852, including 458 children under 10 years of age. The total number of patients receiving humanitarian aid rose from 2119 to 14 579 (Table 2). Importantly 6 governments, Senegal, Egypt, Sri Lanka, Nigeria, Armenia and Kenya, have made commitments to increase their support of in-country haemophilia programmes.

In 2016, treatment of acute bleeding episodes represented the single largest category of utilization, followed by prophylaxis and surgery (Figure 3A and B). Surgeries fell off later in the year, likely due to completion of some backlogged reconstructive orthopaedic and circumcision cases (Figure 3C).

By year end 2016, 42 195 acute bleeding episodes had been treated, which included 3% intracranial and 2% intra-abdominal bleeding sites, considered life-threatening (Figure 3B). Of the 675 surgeries reported, 7% were for pseudotumors and 3% were for intracranial haemorrhages (Figure 3C), both considered as life-saving or limb-saving procedures.

4 | DISCUSSION

In 2016, an unprecedented supply of clotting factors was donated in the first full year of the expanded programme. The WFH HAP collected utilization data show very large increases in product use across all treatment populations. Humanitarian aid has transformed from variable and unpredictable donations to a sustainable programme in which almost half the bleeding episodes that were treated between 1996 and 2014 were treated in 2016 alone.

The aid reached 58 of the 73 countries with <1 I.U. per capita FVIII and the number of patients that benefited increased to 14 579, almost 7 times the number of patients treated in 2014, or approximately 10% of the patients globally who had no access to treatment. The increased volume of available products with long shelf life made it possible to

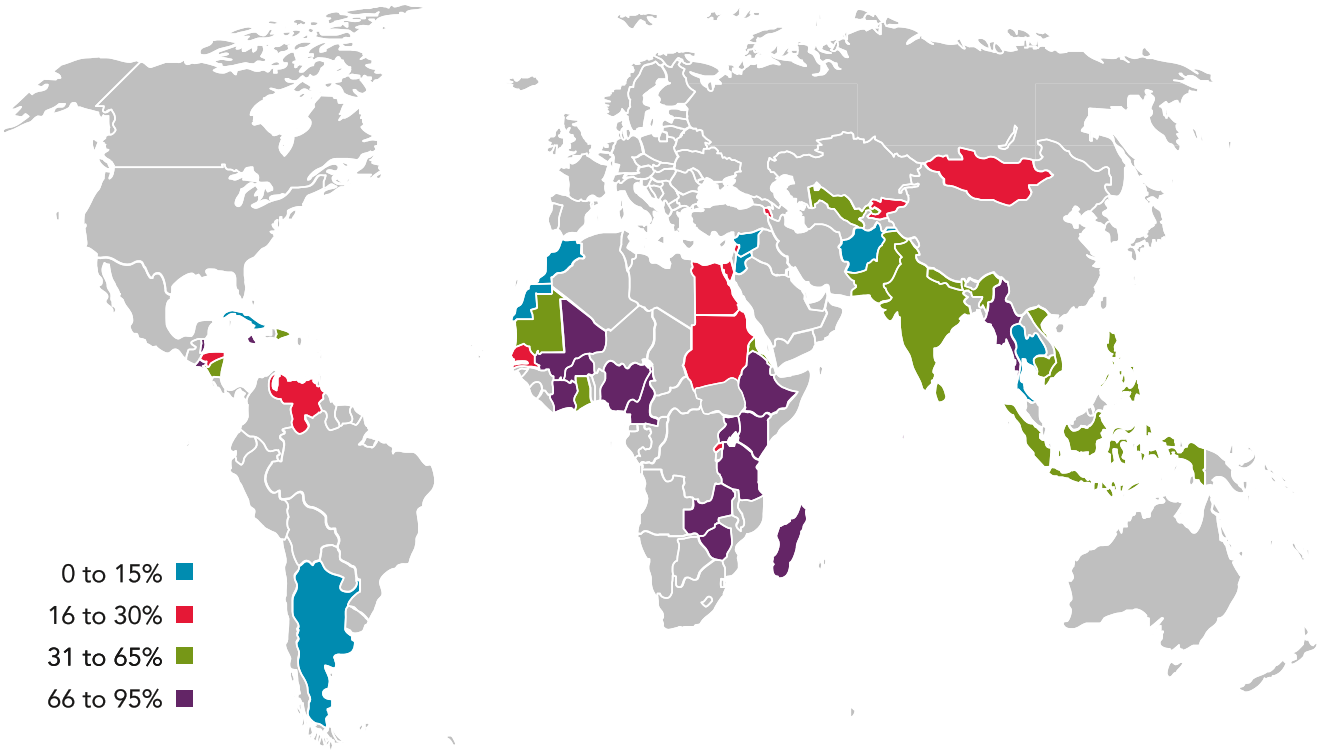

FIGURE 2 Countries reached and percentage of PWH from those countries receiving humanitarian aid in 2016

TABLE 2 Key Performance Indicators (KPI) for product utilization before and after expansion of the WFH Humanitarian Aid Programme

KPI	2014	2016	Fold above 2014
Operational metrics (utilization and process)			
Patients treated by HA donations	2119	14 579	5.9
Total donation in MIUs	21	144	5.9
Number of countries receiving donations	49	58	1.8
Average age of PWH receiving treatment	n/a	20	
Total number of infusions	n/a	61 232	
Impact metrics			
Number of countries doing surgeries	3	22	6.3
Total number of surgeries	21	795	37
Number of acute bleeds treated	6153*	42 195	6.9
Number of PWH on prophylaxis	0	852	n/a
Number of PWH on prophylaxis under 4 years	0	139	n/a
Number of PWH on prophylaxis over 4 and under 10 years	0	319	n/a
Activity metrics (Trainings and reporting)			
Number of attendees of HA workshops	0	335	n/a

HA, Humanitarian Aid; MIU, millions of I.U.s; PWH, persons with haemophilia; n/a, not applicable.
*Estimate.

develop treatment plans which go beyond acute treatment of individual patients in life-threatening situations. This is clear from the number of patients who received surgery, which increased almost 37-fold and included corrective surgery instead of surgery only for life-threatening situations. Furthermore, the WFH has promoted a policy for low-dose prophylaxis in children in the WFH HAP programme, because many studies have demonstrated that treatment for bleeding does not prevent joint disease and that the costs for prophylactic therapy are similar to episodic treatment producing considerably inferior results.[13-15] When transition to prophylaxis is made, it has led to less use of product for acute bleeding, which should be reflected in reporting in future years.

Challenges within HTCs in the recipient countries are high, and include lack of laboratory instrumentation and lack of requisite lab reagents.[16,17] The influx of 10-100-fold more clotting factor into many countries has necessitated the need for new training programmes for the haematologists, surgeons and nurses, as well as laboratory personnel, for management of patients receiving ongoing infusions.

In these environments, there is a predilection to treat only major emergency bleeding episodes and a reluctance to start young children on low-dose prophylaxis or immune tolerance therapy due to fear that a sufficient supply of product will be unpredictable. However, increased confidence in the continuing prospective availability of sufficient clotting factor is an incentive to improve care and management, and importantly, to perform outreach clinics and diagnose many new cases that now still die from bleeding.[18-20] HTCs are instructed to keep records and report on the usage of every donated vial. Currently, 68% of all donated product in 2016 have been reported; some product has not yet been utilized.

A programme of this scope and magnitude has significant limitations. Although product is being distributed to 58 countries under 1 I.U. per capita FVIII, another 15 countries in this category lack sufficient infrastructure to benefit from the programme. This is due to a lack of haemophilia-specific medical expertise and as a consequence no identified patients. In addition, home care therapy has not yet become a standard of practice, and many patients are unable to benefit as they lack access the treatment centre due to distance or transportation constraints. Crucial for the continuation of the HA programme is closing the circle between donation and treatment. The WFH wants to create a reliable and complete system in close collaboration with the centres that are benefitting from the programme.

It is important to recognize that the WFH HAP is a means towards the end. This programme cannot begin to match the treatment guidelines established in Europe, Australia/New Zealand and North America, which include sufficient prophylaxis to prevent nearly all bleeding episodes (>7 I.U. per capita). The programme can, however, improve and save lives of individual patients, provide the impetus for expanded case finding to diagnose and treat more patients and promote government support of HTCs in the recipient countries. This in turn will provide a more receptive environment for treatment innovations that may be available in the future, including gene therapy. This paradigm of securing government commitments has successfully worked at smaller scale with capacity building programmes in the WFH Global Alliance for Progress (GAP).[21]

Outcome data which reflect the management of patients are not currently being collected. In 2018, the WFH will initiate outcome data

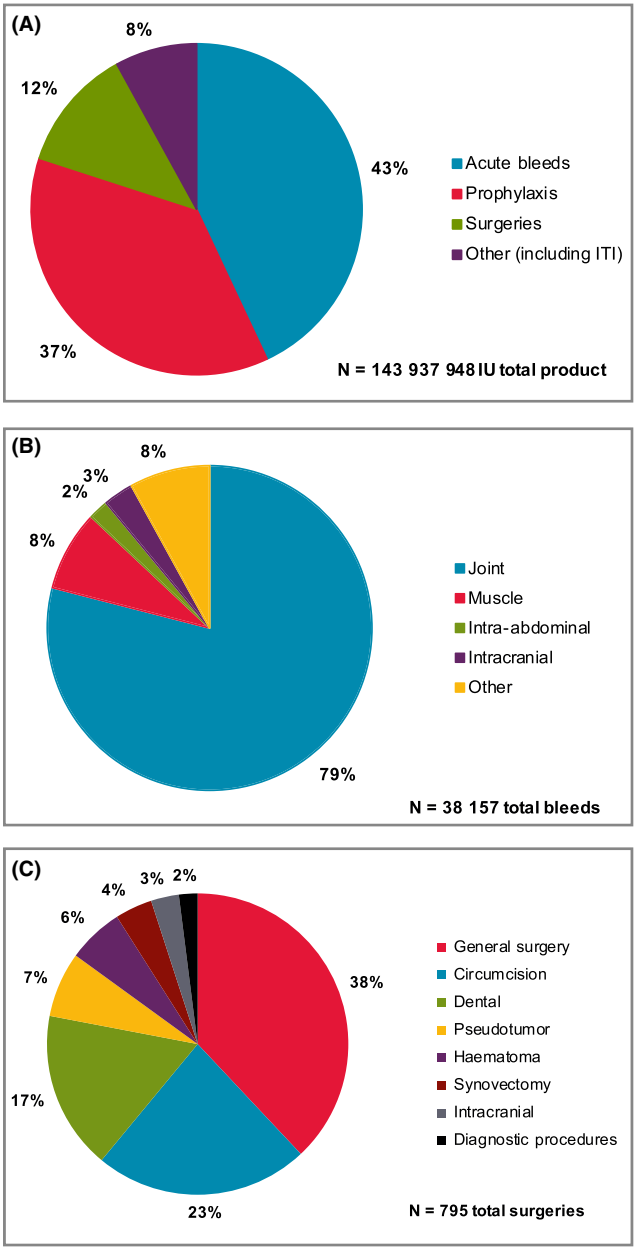

FIGURE 3 A, Reasons for treatment with donated product in 2016. B, Acute bleed types treated in 2016. C, Types of Surgeries performed in 2016

collection of individual patients through a new project the World Bleeding Disorders Registry (WBDR).[22] While it will be worldwide and applicable to all levels of economic development, it is also intended to capture outcome data from many of the HTCs receiving humanitarian aid through collection of anonymous individual patient data following informed consent.

One question that arises is whether donations of ~130 million I.U. per year are sufficient. As the prevalence of identified cases in the countries receiving the donations is generally very low and few patients are on prophylaxis or home care therapy, supply appears to be adequate at present. However, with increasingly more aggressive treatment of bleeding, low-dose prophylaxis, development of home treatment and increasing numbers of new patients, demand will outstrip supply. If increased quantities were available, expansion of low-dose prophylaxis to more patients would be a high priority.

Towards this end, numerous models of corporate partnerships have been successfully explored in recent years within the pharmaceutical company and disaster relief settings.[23-25] While these ventures likely are not all purely altruistic, both pharma executives and academicians have concluded it is both good business sense and a corporate responsibility to collaborate with non-profits to alleviate human suffering. With improved manufacturing technologies, costs of protein production are low, and the yearly donations still amount to a very small proportion of total yearly sales of clotting factor (<2%). As only a minority of manufacturers donate product, much more recognition of these dual mutually beneficial goals is needed. For the biopharma companies supporting the expanded WFH HAP the scope coupled with the financial magnitude of the programme is unprecedented in global health care.[26]

ACKNOWLEDGEMENTS

We would like to thank Bioverativ, Sobi, Grifols, CSL Behring, the Canadian Blood Services, Biotest, and Korean Green Cross for their prospective donations. We would like to acknowledge the ongoing financial contributions from Bioverativ and Sobi for operational and logistical aspects of the WFH HAP. We thank Tanya Dranzewski for programme support, and Christine Herr for graphics assistance. We appreciate ongoing programmatic insights from Alain Baumann, Alain Weill, and Mark Skinner. The WFH HAP comprises a joint collaboration with WFH USA.

DISCLOSURES

The authors have no relevant conflicts to disclose. All authors are affiliated with the WFH. AH and GA are employees. GFP, FP, SD, MEE and HMVB serve as volunteers on the Board of Directors.

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How to cite this article: Pierce GF, Haffar A, Ampartzidis G, et al. First-year results of an expanded humanitarian aid programme for haemophilia in resource-constrained countries. *Haemophilia*. 2018;24:229–235. https://doi.org/10.1111/hae.13409