One million haemopoietic stem-cell transplants: a retrospective observational study

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Summary

Background **The transplantation of cells, tissues, and organs has been recognised by WHO as an important medical task for its member states; however, information about how to best organise transplantation is scarce. We aimed to document the activity worldwide from the beginning of transplantation and search for region adapted indications and associations between transplant rates and macroeconomics.**

Methods **Between Jan 1, 2006, and Dec 31, 2014, the Worldwide Network for Blood and Marrow Transplantation collected data for the evolution of haemopoietic stem-cell transplantation (HSCT) activity and volunteer donors in the 194 WHO member states.**

Findings **953 651 HSCTs (553 350 [58%] autologous and 400 301 [42%] allogeneic) were reported by 1516 transplant centres from 75 countries. No transplants were done in countries with fewer than 300 000 inhabitants, a surface area less than 700 km², and a gross national income per person of US$1260 or lower. Use of HSCT increased from the first transplant in 1957 to almost 10 000 by 1985. We recorded a cumulative total of about 100 000 transplants by 1995, and an estimated 1 million by December, 2012. Unrelated donor registries contributed 22·3 million typed volunteer donors and 645 646 cord blood products by 2012. Numbers of allogeneic HSCTs increased in the past 35 years with no signs of saturation (R^2=0·989). Transplant rates were higher in countries with more resources, more transplant teams, and an unrelated donor infrastructure.**

Interpretation **Our findings show achievements and high unmet needs and give guidance for decisions; to grant access for patients, to provide a donor infrastructure, and to limit overuse by defining risk and region adapted indications for HSCT as an efficient and cost-effective approach for life-threatening, potentially curable diseases.**

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Introduction

WHO has recently recognised the broad idea of provision of medical products of human origin as an important global medical task.[1] The transplantation of cells, tissues, and organs has extended the lifespan of hundreds of thousands of patients worldwide and enhanced their quality of life. As part of this success, the availability of products and procedures has decreased; expectations of patients in need have triggered organ trade and stem cell tourism. As a consequence, guidelines by WHO declare that regulation of transplantation on a national level is a governmental responsibility.[1–5] Data collection and data analysis have been recognised as integral parts of the treatment to achieve efficient and cost-effective use of resources. Harmonised data for use and trends worldwide are a key prerequisite.[6,7] Information about how to best support introduction of HSCT and how this technique has spread remains scarce. Traditional methods of health technology assessment are likely to fail in view of the vast heterogeneity of approaches and small number of transplantation studies being done.[8,9]

Haemopoietic stem-cell transplantation (HSCT) is an established but complex treatment for selected patients with severe congenital or acquired disorders of the haemopoietic system[10–12] and some other life-threatening disorders. Achievements with HSCT have stimulated research in the biology, property, and functions of stem cells, and treatment of cancer generally. Novel technologies to generate, expand, and maintain stem and precursor cells create hope for custom tailored stem cells. Ideas for use range from single organ disease to trauma repair or partial organ replacement.[13–16] HSCT has evolved from experimental bone marrow transplantation more than half a century ago to an accepted and successful treatment; therefore, the long experience and past errors and successes might serve to improve access for all patients in need and as guidance for the application of medical products of human origin generally.

The Worldwide Network for Blood and Marrow Transplantation (WBMT), an HSCT umbrella organisation recognised by WHO as a non-governmental organisation, has taken up the task of helping with HSCT worldwide. On the occasion of the one millionth transplant at the end of 2012, we present the worldwide diffusion of HSCT from its beginning up to now.[17]

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For more on **WBMT** see www.wbmt.org

For more on the **World Marrow Donor Association** see www.marrowdonor.org

See Online for appendix

Methods

Patients and study design

In this retrospective observational survey we analysed the number of HSCTs worldwide from the first published series (to the best of our knowledge) of bone marrow transplants in 1957[18] to Dec 31, 2012 (table 1). Data for HSCT were collected by WBMT through its network of international or regional member organisations; data for registered unrelated donors, on registered cord blood products and on their use were collected through the World Marrow Donor Association. The organisations providing the information to the WBMT were: Australasian Bone Marrow Transplant Recipient Registry (ABMTRR), African Blood and Marrow Transplantation Group (AFBMT), Asian Pacific Blood and Marrow Transplantation Group (APBMT), Bone Marrow Donors Worldwide (BMDW), Canadian Blood and Marrow Transplantation Group (CGBMT), the Center for International Blood and Marrow Transplant Research (CIBMTR), European Society for Blood and Marrow Transplantation (EBMT), Eastern Mediterranean Blood and Marrow Transplantation Group (EMBMT), Latin American Blood and Marrow Transplantation Group (LABMT), and the World Marrow Donor Association (WMDA).

Main outcome measures were the spread of HSCT over time and transplant by donor type, country of origin, and WHO region. Secondary outcome measures were to document any trends in the number of transplantations by donor type or region, to classify these trends, and quantify differences in the use of autologous or allogeneic HSCT across indications and regions, and classification of the countries in the international exchange of donors and cord blood products.

No individual patient data were used; no ethics committee approval was mandated.

Data collection and validation

Global transplant numbers by country of origin, year of transplant, and donor type (autologous [ie, a transplant with the patient's own cells] *vs* allogeneic [ie, with cells from a healthy donor, family or unrelated]) were searched for in 194 WHO member states (appendix pp 4–11) through the reporting member organisation either in paper form or electronically. Data were collected from the scientific literature for very early transplants.[18–21] Detailed and validated information about main indication, stem cell source, and allogeneic donor type were obtained for the years 2006 to 2010. Data were collected by the participating organisations so patient de-identification was not necessary. Data were validated by crosschecking for double reporting between the participating institutions and by onsite visits to selected teams to verify reported data as part of the

	1957–70	1971–85	1986–91	1992–95	1996–2005	2006–12	Total
Pan-American total	..	2422	14975	33734	126212	119140	296754 (31%)*
Allogeneic	..	2375 (98%)†	7242 (48%)†	12092 (36%)†	51347 (41%)†	54437 (46%)†	127764
Autologous	..	47	7733	21642	74865	64703	168990
South East Asian and Western Pacific total	..	505	3349	9120	53763	73342	140079 (15%)†
Allogeneic	..	450 (89%)†	2508 (75%)†	5061 (55%)†	30340 (56%)†	44607 (61%)†	82966
Autologous	..	55	841	4059	23423	28735	57113
Eastern Mediterranean and African total	..	33	300	441	5104	9625	15503 (2%)*
Allogeneic	..	32 (97%)†	239 (80%)†	357 (81%)†	3821 (75%)†	5968 (62%)†	10417
Autologous	..	1	61	84	1283	3657	5086
European total	..	6088	21152	35660	222470	215941	501315 (53%)*
Allogeneic	..	4165 (68%)†	10570 (50%)†	12869 (36%)†	68970 (31%)†	82576 (38%)	179154
Autologous	..	1923	10582	22791	153500	133365	322161
Total							
Allogeneic	275 (100%)†	7022 (78%)†	20559 (52%)†	30379 (38%)†	154478 (28%)†	187588 (45%)†	400301 (42%)*
Autologous	0	2026	19217	48576	253071	230460	553350
Total HSCT	275	9048	39776	78955	407549	418048	953651 (100%)*
Cumulative numbers of unrelated donors	..	0	741994	1998172	10777966	22346551	..
Cumulative numbers of cord blood products	..	0	0	2345	275669	645646	..

Data are total HSCT by main donor type (allogeneic or autologous HSCT), during the respective timeframe, by WHO region, and the development of cumulative numbers of registered unrelated donors and cord blood products during the same time. All regions are WHO-defined regions. Retrospective allocation of transplants to the respective WHO region is not possible in details. Most procedures were done in the USA and in Europe. HSCT=haemopoietic stem-cell transplantation. *Represents column percentages of total HSCT per WHO region. †Represents proportion of allogeneic HSCT during the respective timeframe in the respective WHO region.

Table 1: **Milestones in the development of HSCT, 1957–2012**

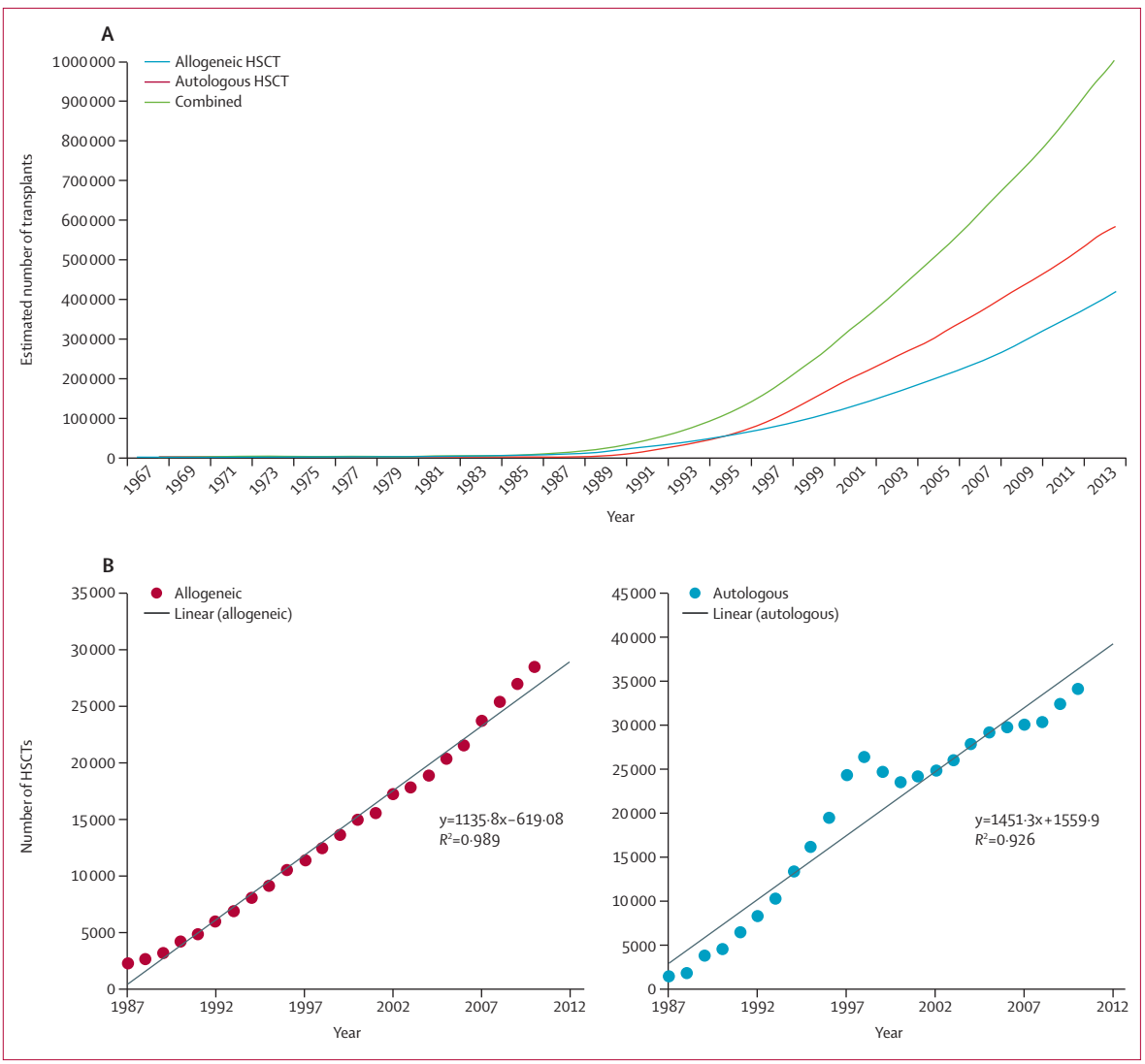

Figure 1: **Global development of HSCT, 1957–2012**
(A) Global development of HSCT by donor type from 1957 to 2012. The one millionth HSCT was estimated to have been done by the end of 2012. (B) Global development of HSCT by donor type from 1987 to 2010 based on retrospective and validated data. HSCT=haemopoietic stem-cell transplantation.

quality control programme within the European and North American organisations. The year 2010 was chosen for the detailed comparison of macroeconomic factors because all internal validations suggested that this dataset was the most complete. The number of potential missing transplant numbers is estimated to be less than 5% for allogeneic HSCT and less than 15% for autologous HSCT. This number is much lower for Australia, Canada, Europe, Japan, and the USA. Missing data for some countries for the years 2011–12, and for years when reporting was not mandatory, were extrapolated considering a 5% increase.

Data for unrelated donor transplants included the presence or absence of unrelated donor registries and public cord blood banks per country, the numbers of registered volunteer donors and of stored public cord blood products, the numbers of unrelated donor HSCT per country and year, and the number of imported, exported, or internally used products (appendix pp 4–11).

Definitions

We computed the frequency of transplant as the number of patients given a first HSCT per 10 million inhabitants; we assessed patients by donor type (allogeneic or autologous HSCT) stem cell source (bone marrow, peripheral blood stem cells, or cord blood) and, for the years 2006–10, detailed indication. There was no adjustment for patients who crossed borders and received their HSCT in a foreign country. We computed team density for each country as the number of teams per 10 million inhabitants in 2010. Team refers to the respective hospital or institution

	Allogeneic			Autologous	Total
	Family	Unrelated	Total		
Leukaemias*	41 615	43 935 (51%)†	85 550 (92%)‡	6970 (8%)‡	92 520 (35%)§
Acute myeloid leukaemia*	19 972	20 257	40 229‖	5352	45 581
Acute lymphoblastic leukemia*	10 291	10 742¶	21 033	842	21 875
Chronic myeloid leukaemia*	3291	2425	5716	32	5748
Myelodysplastic and myeloproliferative neoplasia*	6247	8191¶	14 438	204	14 642
Chronic lymphocytic leukaemia*	1533	1836¶	3369	493	3862
Other leukaemia*	281	484¶	765	47	812
Lymphoproliferative disorders	9421	8006 (46%)†	17 427 (13%)‡	120 959 (87%)‡	138 386 (53%)§
Plasma cell disorders	2483	1622	4105	61 266	65 371
Hodgkin's disease and non-Hodgkin lymphoma	6938	6384	13 322	59 693	73 015
Solid tumours	467	255 (35%)†	722 (8%)‡	12 901 (92%)‡	13 623 (5%)§
Non-malignant disorders*	8614	5711 (40%)†	14 325 (92%)‡	1176 (8%)‡	15 501 (6%)§
Bone marrow failures*	4727	2635	7362	10	7372
Haemoglobinopathies*	2176	512	2688	10	2698
Immune deficiencies*	1144	1364¶	2508	24	2532
Inherited diseases of metabolism*	309	683¶	992	17	1009
Autoimmune disorders	57	47	104‖	1058	1162
Other non-malignant disorders*	201	470¶	671	57	728
Others§	335	423 (56%)†	758	237	995
Total	60 452 (51%)	58 330 (49%)†	118 782 (46%)‡	142 243 (54%)‡	261 025

Appendix shows the list of participating teams. *Significantly more allogeneic than autologous haemopoietic stem-cell transplantation (HSCT) for this indication (p<0·0001). †Proportion of patients with an unrelated donor allogeneic HSCT. ‡Proportion of patients with an allogeneic or autologous HSCT. §Column percentages. ¶Significantly more unrelated than family donors in allogeneic HCST for this indication (p<0·0001). ‖Neutral distribution between family donors and unrelated donors for allogeneic HSCT.

Table 2: **Global numbers of HSCT by main indication and donor type undertaken by 1516 teams in 75 countries, 2006–10**

doing HSCT and was defined as reported by the participating organisation. International transplants were defined as those in which a patient received cells from an unrelated donor living in a country different from the recipient. The allocation of individual countries to a region followed the WHO regional offices classification and the previously reported restriction to four regions (appendix pp 4–11).[22,23]

For **WHO region classification** see www.who.int/about/regions/en/

Information about population data and gross domestic product per person, gross national income per person, and health-care expenditures per person (appendix pp 12–14) were obtained from the World Bank. Information about the Human Development Index was obtained from the UN Human Development Report. Information about country size was obtained from the World Atlas.

For **data from the World Bank** see http://www.worldbank.org

For the **UN Human Development Report** see http://hdr.undp.org/en/statistics/hdi

For **data from the World Atlas** see http://www.worldatlas.com

Statistical analysis

The data analysis was comprised of ordinary least squares regressions for trends, χ^2 tests for independent proportions of indications, and binomial tests for donor type. Calculations were done in Eviews8 and Excel 2010 (Microsoft).

Role of the funding source

The funding source had no role in the study design, in the collection, analysis, or interpretation of the data, and in the writing of the report. The corresponding author had full access to all of the data and had the final responsibility to submit for publication.

Results

Numbers of HSCT increased after an initial period of limited activity continually to 10 000 HSCTs worldwide by 1985, to roughly 50 000 by 1991, to about 100 000 by 1995, to roughly 500 000 by 2005, and doubled to about 1 million by December, 2012 (table 1 and figure 1A). When HSCT first started, this technique was restricted to a few countries (appendix pp 4–11). By the end of 2012, HSCT had spread slowly but steadily to 75 countries; 35 started with allogeneic HSCT, 23 with allogeneic and autologous HSCT together, and 17 with autologous HSCT.

Information for 953 651 patients with HSCT (400 301 [42%] allogeneic and 553 350 [58%] autologous) collected by 1516 transplant centres from 75 countries over five continents during the whole timespan forms the basis of this report (table 1). In 2010, transplants were undertaken in 71 of the 194 WHO member states with allogeneic HSCT only in two, autologous HSCT only in five, and both in 64 (appendix pp 4–11). On the basis of the extrapolations in some countries with missing data and annual growth pattern, we estimate that the millionth HSCT took place by the end of 2012 (figure 1). Numbers of HSCT differed by WHO region, with the highest number of HSCT reported from Europe (501 315 [52%], of which 179 154 were allogeneic

[45%]), followed by the Americas (296 754 [31%]; 127 764 allogeneic [32%]), southeast Asia and western Pacific (140 079 [15%]; 82 966 allogeneic [21%]), and eastern Mediterranean and Africa (15 503 [2%]; 10 417 allogeneic [2%]; table 1). No transplants were done in countries with a population of fewer than 300 000 inhabitants, with a surface area of less than 700 km², and a gross national income per person of lower than US$1260.

The number of HSCTs increased over time with differences in onset, type, and speed of diffusion in all WHO regions (table 1 and appendix pp 17–21). However, the relative number of transplants between the WHO regions varied significantly over time (p<0·0001). The proportion of allogeneic compared with autologous HSCT was descriptively different between regions, with Africa and the eastern Mediterranean region initially having substantially more allogeneic transplants than autologous transplants. However, there are no substantial differences in the ratio of allogeneic to autologous transplants between regions over time (p=0·99), hence the regional differences do not depend on time. The proportion of all allogeneic HSCT in southeast Asian and western Pacific WHO region also differs significantly from the combined relative level in Americas and Europe combined (p<0·0001) and over all time periods (p<0·0001). Equally, the share of allogeneic in total HSCT differs significantly between the the Americas and Europe (p<0·0001).

The spread of allogeneic HSCT grew for all regions with the exception of the Americas (figure 1B and appendix pp 15, 17–21). Increments were higher in countries with higher gross national income per person and highest in the five countries with the highest numbers of HSCT in 2010 (France, Germany, Italy, Japan, and the USA; appendix p 17). Thus, the gap in allogeneic transplant numbers is still widening between the regions. Uptake of autologous HSCT started later and showed different growth patterns from allogeneic transplant, depending on WHO region and year of study. A clear pattern of saturation emerges in the Americas and in Europe and linear increases or growth in the other regions. Saturation is indicated by recent decreases in growth (table 1 and appendix pp 4–11, 15). Because the potential for missing data for HSCT is lower in the Americas and in Europe than other regions, the difference in diffusion patterns is unlikely to be affected by uncaptured data.

Numbers of countries with registries increased from two in 1987 to 57 in 2012, numbers of registered donors increased from 3072 in 1987 to 22 346 551 in 2012. Cord blood banks were first established in 1993 in two countries, then increased to 18 in 2000 and to 36 in 2012 with 645 646 registered human leucocyte antigen typed, cryopreserved cord blood products (table 1 and appendix pp 4–11).Use of unrelated donors increased over time and exceeded family donor transplants in 2006, accompanied by an increase of international transplants across borders to more than 10 000 per year between 2006 and 2012; so did the exchange of cord blood products (appendix pp 4–11). Use of unrelated donor HSCT and increase in donor availability paralleled each other. The high share of the variation explained by time alone (R^2=0·989) precludes a statement on which trend triggered the other and renders any estimation of an association with additional macroeconomic factors difficult.

We recorded significant differences in HSCT activity within the use of donor type, indications for HSCT, and WHO regions (tables 2, 3, and 4). The proportions of allogeneic HSCT for leukaemias and lymphoproliferative disorders were not different across the Americas and Europe (p=0·93) but differed between the Americas plus Europe combined versus the southeast Asian and western Pacific region and between the Americas plus Europe and the Eastern Mediterranean and African region (both comparisons p<0·0001), and between southeast Asian and western Pacific region and the

	Allogeneic				Total
	AMR	SEAR/WPR	EMR/AFR	EUR	
Leukaemias	24 586 (28%)	22 257 (26%)	2341 (2%)	36 366 (42%)	85 550 (100%)
Acute myeloid leukaemia	11 734	10 859	1064	16 572	40 229
Acute lymphoblastic leukaemia	5504	6199	728	8602	21 033
Chronic myeloid leukaemia	1591	1753	339	2033	5716
Myelodysplastic and myeloproliferative neoplasia	4100	2751	196	7391	14 438
Chronic lymphocytic leukaemia	1477	110	14	1768	3369
Other leukaemia	180	585	0	0	765
Lymphoproliferative disorders	5867 (33%)	2705 (16%)	165 (1%)	8690 (49%)	17 427 (100%)
Plasma cell disorders	1091	325	52	2637	4105
Hodgkin's disease and non-Hodgkin lymphoma	4776	2380	113	6053	13 322
Solid tumours	97 (13%)	257 (36%)	4 (0%)	364 (50%)	722 (100%)
Non-malignant disorders	4085 (28%)	3385 (23%)	1593 (10%)	5262 (39%)	14 325 (100%)
Bone marrow failures	2142	2012	742	2466	7362
Haemoglobinopathies	518	626	546	998	2688
Immune deficiencies	716	266	245	1281	2508
Inherited diseases of metabolism	349	133	57	453	992
Autoimmune disorders	26	11	3	64	104
Other non-malignant disorders	334	337	0	0	671
Others	216	180	26	336	758
Total	34 851 (29%)	28 784 (24%)	4129 (3%)	51 018 (43%)	118 782 (100%)

The appendix shows the list of participating teams. Percentages represent row percentages. There were significant differences between the regions concerning indications for allogeneic HSCT for both groups and subgroups (p<0·0001), and between all regions (pairwise). HSCT=haemopoietic stem-cell transplantation. AMR=Pan-American WHO region. SEAR/WPR=southeast Asian and western Pacific WHO region. EMR/AFR=eastern Mediterranean and African WHO region. EUR=European WHO region.

Table 3: **Global numbers of allogeneic HSCT by main indication and WHO region undertaken by 1516 teams in 75 countries, 2006–10**

	Autologous				Total
	AMR	SEAR/WPR	EMR/AFR	EUR	
Leukaemias	1319 (19%)	1164 (16%)	219 (3%)	4268 (61%)	6970 (100%)
Acute myeloid leukaemia	1141	929	185	3097	5352
Acute lymphoblastic leukaemia	114	154	4	570	842
Chronic myeloid leukaemia	1	5	0	26	32
Myelodysplastic and myeloproliferative neoplasia	16	14	16	158	204
Chronic lymphocytic leukaemia	37	25	14	417	493
Other leukaemia	10	37	0	0	47
Lymphoproliferative disorders	37158 (31%)	14982 (12%)	2029 (2%)	66790 (55%)	120959 (100%)
Plasma cell disorders	19719	7088	852	33607	61266
Hodgkin's disease and non-Hodgkin lymphoma	17439	7894	1177	33183	59693
Solid tumours	3238 (25%)	2429 (19%)	187 (1%)	7047 (54%)	12901 (100%)
Non-malignant disorders	224 (19%)	150 (13%)	10 (1%)	792 (67%)	1176 (100%)
Bone marrow failures	4	2	0	4	10
Haemoglobinopathies	0	5	0	5	10
Immune deficiencies	5	2	0	17	24
Inherited diseases of metabolism	0	1	0	16	17
Autoimmune disorders	174	124	10	750	1058
Other non-malignant disorders	41	16	0	0	57
Others	35	92	0	110	237
Total	41974 (29%)	18817 (13%)	2445 (1%)	79007 (56%)	142243 (100%)

The appendix shows the list of participating teams. Percentages represent row percentages. AMR=Pan-American WHO region. SEAR/WPR=southeast Asian and western Pacific WHO region. EMR/AFR=eastern Mediterranean and African WHO region. EUR=European WHO region.

Table 4: **Global numbers of autologous haemopoietic stem-cell transplantation by main indication and WHO region undertaken by 1516 teams in 75 countries, 2006–10**

Eastern Mediterranean and African region (p<0·0001). There were significant differences between the regions concerning indications for autologous HSCT (p<0·0001), and between all regions (pairwise). We noted no support for equal distribution in indications for autologous HSCT across the Americas and Europe.

Absolute numbers of HSCT in the 75 participating countries in 2010 ranged from four to 17230 for all HSCTs (figure 2A); they ranged from one to 7763 HSCTs for allogeneic and from six to 9467 HSCTs for autologous HSCT. Allogeneic HSCTs were done at some stage over the years in 70 countries, autologous HSCT in 72 countries. Allogeneic HSCTs from unrelated donors were done in 2010 in 50 countries; absolute numbers ranged from one to 3698 HSCTs. Cord blood transplants were done in 2010 in 44 countries; absolute numbers ranged from one to 973 HSCTs. Numbers of transplant centres ranged from one to 381 centres per country with team densities from 0·1 to 31·3 teams per 10 million inhabitants.

Total transplants in 2010 ranged from 0·4 to 962 (median 163) per 10 million inhabitants (figure 2B). They ranged from 0·4 to 506 (median 57·6) for allogeneic and from six to 560 (median 95·3) for autologous HSCT (appendix pp 22–23). We noted substantial differences between countries and regions related to the use of unrelated donors and unrelated cord blood products. Some countries made use of their unrelated donors and cord blood products mainly within the country; others imported more than exported or exported more than imported (figure 2C). The proportion of transplants per 10 million individuals were higher in countries with greater gross domestic product per person (n=182, R^2=0·4391; allogeneic n=182, R^2=0·3692; autologous n=182, R^2=0·4552), greater gross national income per person (n=177, R^2=0·6021; allogeneic n=177, R^2=0·5232; autologous n=177, R^2=0·5981; figure 3), greater health care expenditures per person (n=188, R^2=0·5306; allogeneic n=188, R^2=0·4562; autologous n=188, R^2=0·5310), a higher Human Development Index (n=186, R^2=0·3885; allogeneic n=186, R^2=0·3337; autologous n=186, R^2=0·3888), more donors (n=193, R^2=0·0924; allogeneic n=193, R^2=0·1252; autologous n=193, R^2=0·0654), and bigger cord blood banks (n=193, R^2=0·1320; allogeneic n=193, R^2=0·1542; autologous n=193, R^2=0·1059).

We did not use a cutoff to categorise these variables but used a continuous scale. The association between transplant and macroeconomic factors varied substantially between donor types, WHO regions, and World Bank categories. We did not do a formal analysis to establish how macroeconomic factors affected transplantation. Financial resources determined by the macroeconomic factors generally showed higher associations with transplant for autologous HSCT than allogeneic HSCT, with no substantial differences for allogeneic family or unrelated donor HSCT. Ease of access to HSCT as determined by team density generally showed higher association for autologous than allogeneic HSCT. Numbers of donors or numbers of cord blood products generally showed a low association with transplants with the exception of the Americas and in countries in the lower middle income World Bank category. Generally, associations between macroeconomic factors and transplant rates were higher in the American and southeast Asian and western pacific region. When we analysed World Bank categories, associations were generally low with a stronger effect of financial resources in the low middle income category and of team density for autologous HSCT in the upper middle income category (appendix pp 12–14).

Discussion

These global findings show striking differences in absolute transplant numbers, frequency of transplant, and spread of HSCT. The different patterns are affected mainly by macroeconomic factors related to availability of resources and infrastructure. We noted major differences in use of autologous and allogeneic HSCT

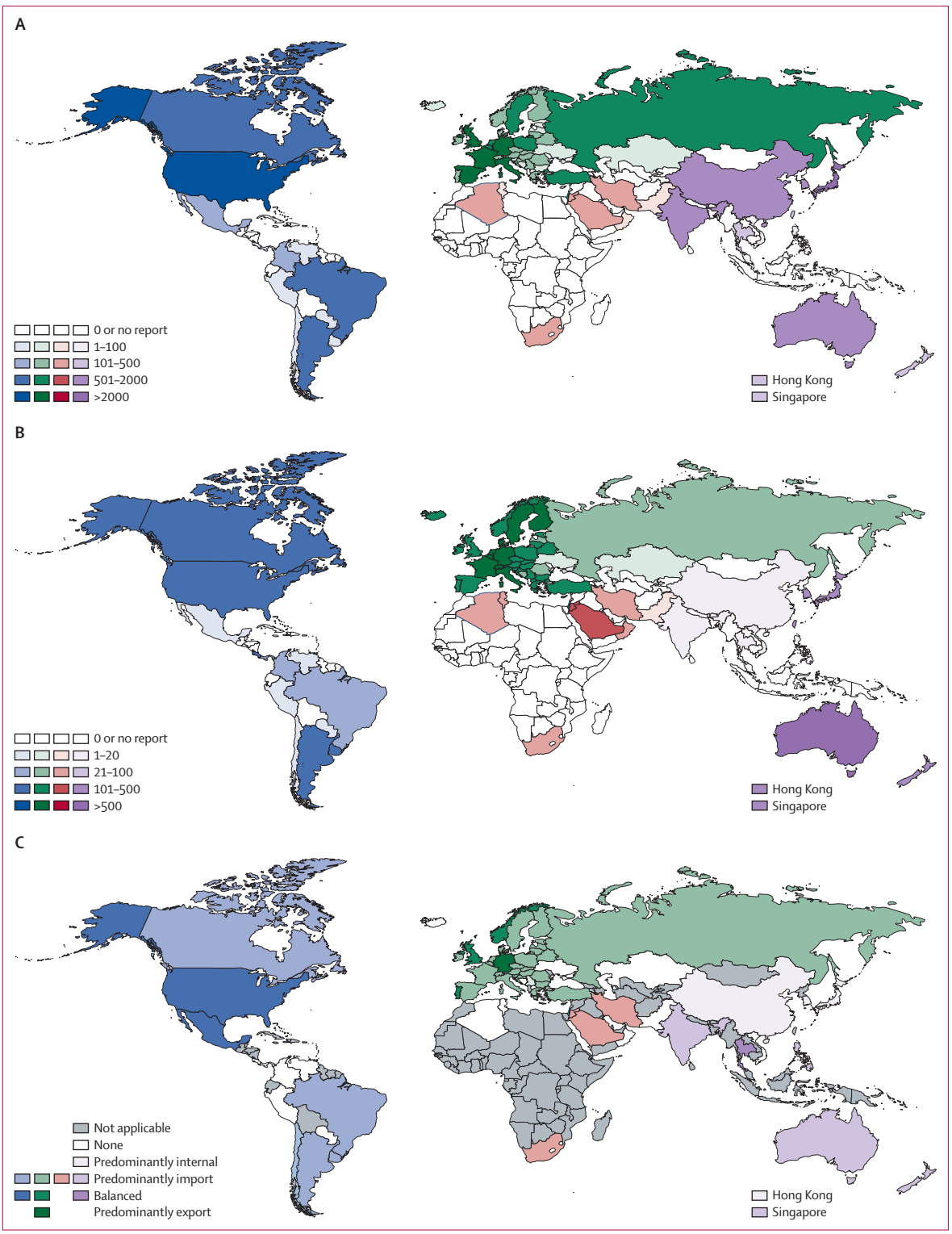

Figure 2: **Global HSCT activity in 2010**

(A) Absolute number of HSCT in participating countries by WHO regional offices area in 2010. Regions are coloured by WHO regional offices area code. Shades of colours show absolute transplant numbers (allogeneic and autologous combined). (B) Frequency of transplant per 10 million people of allogeneic and autologous HSCT combined in participating countries by WHO regional offices area in 2010 as reported from the prospective survey 2006–10. Regions are coloured by WHO regional offices area code. (C) Use of unrelated donor HSCT in participating countries. Colours show import, export, or balanced use. HSCT=haemopoietic stem-cell transplantation.

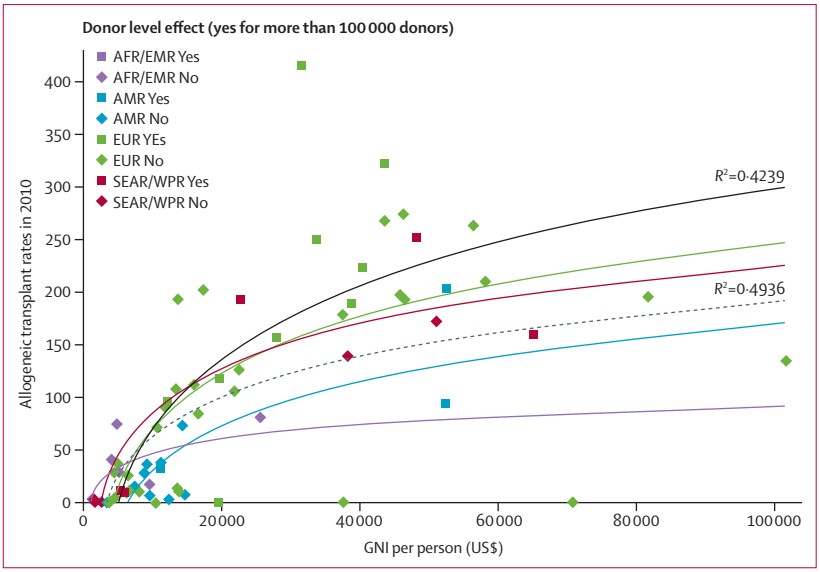

Figure 3: **Transplants in WHO member states in 2010 and selected macroeconomic factors**
The graphic depicts all countries in which transplants were done in 2010, transplants per 10 million people for allogeneic haemopoietic stem-cell transplantation in 2010, and their GNI per person. Colours represent the WHO regional offices area code with their respective trend lines. Black lines represent trend lines of countries with (unbroken line) more than 50 000 registered unrelated donors and with (broken line) no registry or less than 50 000 donors. EMR/AFR=eastern Mediterranean and African WHO region. AMR=Pan-American WHO region. EUR=European WHO region. SEAR/WPR=southeast Asian and western Pacific WHO region. GNI=gross national income.

Panel: Research in context

Systematic review

The major organisations in the specialty of haemopoietic stem-cell transplantation (HSCT) from the five continents Africa, America, Asia, Australia, and Europe systematically analysed the transplant situation in all WHO member states within their capture area by teams doing HSCT from the beginning of HSCT. They were responsible for screening the scientific literature in all languages within their respective region on reports about "bone marrow transplantation" from 1957 (the time of the, to our knowledge, first systematic report about bone marrow transplantation in human beings),[19] onwards. Information about international unrelated transplants was systematically analysed by the World Marrow Donor Association through their affiliated members and comprises all unrelated donor registries and unrelated cord blood banks since the establishment of the first unrelated donor registry in 1973. The review probably captured more than 95% of all allogeneic and more than 90% of all autologous HSCT worldwide. It did not capture so-called stem-cell treatments by non-scientific dubious institutions.

Interpretation

Evolution of HSCT, current absolute transplant numbers, transplant rates, and proportions of donor types vary significantly between countries and WHO regions. These differences relate partly to macroeconomic factors such as surface and population size of the country or their resources and infrastructure. The number of allogeneic HSCTs increased in all regions of the world without any signs of saturation; by contrast, numbers of autologous HSCT seem to plateau in some regions, suggesting underuse of allogeneic and risk of overuse of autologous HSCT. Competent authorities are challenged to provide a locally adapted regulatory framework, professional organisations to provide evidence as to the indications for HSCT compared with any non-transplant strategy regarding survival, quality of life, and costs, depending on the economic situation of the respective region or countries. HSCT is no longer an experimental treatment. There is a need for national unrelated donor registries.

(panel). Global numbers of allogeneic HSCT increased with no signs of saturation but substantial differences between regions were present. Of note, increase in absolute numbers was highest in those five countries with the highest numbers of HSCT. The lack of saturation shows underuse and suggests that more patients would have been treated by HSCT had they had access and had donors been available.

Evolution of the use of autologous HSCT showed a different pattern and different needs. Autologous HSCT developed later than allogeneic HSCT but increased rapidly and even outnumbered allogeneic HSCT in Europe and North America up to 1998. Numbers suddenly dropped when prospective studies failed to identify a clear advantage for patients with breast cancer and some other solid tumours compared with a non-transplant strategy.[24–26] Present data suggest a trend for saturation in Europe and America. The association of transplant rate with team density might suggest a tendency for overuse; autologous HSCT might be done without stringent indication when infrastructure and resources are available. Looking back an what has come before helped identify errors and paved the way of today success. None of the six patients reported in 1957 and only three of 203 patients in 1970 survived.[19,20] However, these data from the first international collaborative study suggested that HSCT could restore lost haemopoietic function, but showed the major obstacles: rejection, graft-versus-host disease, toxic effects of the conditioning regimen, and relapse of the underlying disease.[27] The proof of concept triggered clinical research and cooperation across borders. Improved outcome led to HSCT at earlier phases than end stage disease,[28] stimulated broader application of HSCT, and induced the search for unrelated donors or cord blood products.[29–33] Data sharing, rapid dissemination of unrelated donor tissue typing data, and concerted actions fostered rapid dissemination. The global exchange of stem-cell products across borders, independent of religion, race, personal beliefs, and independent of patents or commercial interests[34–36] was helped by the establishment of joint quality management systems through partner organisations FACT, JACIE, WMDA, and Bone Marrow Donors Worldwide, and by the cooperation with national competent authorities and with WHO on the global level through WBMT. The basic ideas include voluntary participation but acceptance of external control through peers.[37–40] This idea fits with the WHO rules for organ, cell, and tissue donation that include data collection and data analysis as integral parts of the treatment.[5]

Our study of the introduction and spread of HSCT presents a more complex view than previous analyses with substantial differences between regions. A minimum of resources needs to be available for introduction and for patients to have access to the treatment. Data do not define the optimum number of teams. Transplants increase with more transplant teams but a minimum number of

transplants is needed for accreditation and there might be a risk of overuse with too many teams.[37,41,42] Hence spread of HSCT was associated with financial resources and transplant infrastructure but to a different extent depending on WHO region and World Bank category and with different patterns of diffusion. Proportions of uncaptured data, estimated to be less than 5% for allogeneic and less than 15% for autologous HSCT, varied between the regions too, and were estimated to be lowest in the regions with the highest absolute numbers. Despite these limitations, missing data are unlikely to change these conclusions. The modest association of donor numbers or cord blood products in most regions might be explained by the free exchange of unrelated products even to countries without their own unrelated donors. Hence, availability of resources, evidence, positive regulatory environment, and expectations were associated with high number of transplants.[34,41]

Competent authorities will have to adapt their regulations to their specific national deficiencies and needs. In small countries, they will face the dilemma of either establishing a local transplant centre (despite small numbers of patients) or sharing responsibility.[41,42] All will be challenged to support donor registries where they do not yet exist and to implement quality control measures. Professional organisations are challenged to foster the network of regional outcome data registries and collaboration in patient networks beyond the transplant itself. No outcome data exist yet in this global report. Still, there are indications that macroeconomic factors affect outcome as well.[37] Evidence-based recommendations for indications should include assessment of disease risk and patient's risk, donor type and donor risk, time course since diagnosis, and potential outcome.[43–45] Recommendations might differ depending on the macroeconomic situation and between regions. HSCT should be done with the best and most cost-efficient transplant technology and offer the best available treatment regarding overall survival, quality of life, and costs compared with any other non-transplant strategy. Cost-effectiveness considerations might favour strategies in countries with limited resources on patients with severe non-malignant disorders and HLA-identical family donors and building up infrastructure, in countries with intermediate resources on patients with low risk transplants and in disease categories where alternative non-transplant strategies are very expensive.

In summary, these data show the effect of intensive global collaboration and data sharing on donors and patient outcome. These results could provide an example for future medical products of human origin[46] and disclose underusing HSCT and the risk of overuse of HSCT. Competent authorities are challenged to provide adequate infrastructure for patients and donors and to change the present situation in which access remains restricted to countries and people with sufficient resources. Professional organisations will have to define the evidence-based but economically adapted indications for HSCT as an efficient and cost-effective approach for patients with life-threatening, potentially curable diseases.

For more on **FACT** see http://www.factwebsite.org/

For more on **JACIE** see http://www.jacie.org/

For more on **WMDA** see http://www.worldmarrow.org/

For more on **Bone Marrow Donors Worldwide** see http://www.bmdw.org/

Contributors

DN, AG, MCP, MA,KB, KF, and FRA designed the study; HB, MCP, MA, AG, DN, KF, MG, MA, LFB, MH, YK, JL, MI, MCP, JP, JS, AM, and KF contributed data and assured quality of the data given to the analysis; HB, MG, KF, MP, and LF analysed data; AG, DN, MCP, and MA drafted the manuscript; DN, MCP, MA, DC, HB, LFB, MH, MI, YK, JL, MO, EG, JP, NN, JvR, LN, AM, KF, MG, AG, and FRA processed the manuscript. European data were derived from the European Society for Blood and Marrow Transplantation (EBMT) database for the years 1965–89 and from the EBMT annual activity survey office since 1990.[21] Non-European data were initially provided by the Center for International Blood and Marrow Transplant Research (CIBMTR) since 1964. They were supplemented or replaced by the surveys of the Asian Pacific Blood and Marrow Transplantation Group (APBMT) since 1974, the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) since 1982, the Eastern Mediterranean Blood and Marrow Transplantation Group (EMBMT) since 1984, the Canadian Blood and Marrow Transplantation Group (CGBMT) since 2002, the Latin American Blood and Marrow Transplantation Group (LABMT) since 2009, and the African Blood and Marrow Transplant Group (AFBMT) since 2010. Unrelated donor and cord blood information were derived from the World Marrow Donor Association (WMDA) and Bone Marrow Donors Worldwide (BMDW).

Declaration of interests

We declare no competing interests.

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