Global blood donor challenges
FIODS/IFBDO meeting
Campus Lucca
6 October 2013

Italian policies for
blood and blood product self-sufficiency in safe

Giuliano Grazzini
Director National Blood Centre
National Institute of Health
Rome, Italy
Overview on:

1) Strategic goals and essential figures of the Italian blood system

2) Italian policies for blood and blood product self-sufficiency

3) Italian policies for blood and blood product quality and safety
Overview on:

1) Strategic goals and essential figures of the Italian blood system

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BLOOD DONATION IN THE WORLD

BY HUMAN DEVELOPMENT INDEX

Donations per 1000 population, by HDI

HDI = Human Development Index

Source: WHO Global Database on Blood Safety (GDBS), 2009 survey
Strategic goals – I  
Law 21 October 2005, n. 219

- Quantitative and qualitative self-sufficiency of blood and blood products (including plasma-derived medicinal products) as a supra-local and supra-regional goal of the NHS.

- Promotion and development of voluntary non-remunerated, regular / repeat blood donation, and VNR donor retention.

- High quality and safety of blood components, transfusion medicine activities and plasma-derived medicinal products.
Strategic goals – II
Law 21 October 2005, n. 219

✓ Achievement of full compliance with national and European regulatory provisions on blood and blood products

✓ Appropriate management and clinical utilization of blood resources (including patient blood management - PBM)

✓ Continuous development of transfusion medicine, aligned with scientific progress

✓ System’s accountability, effectiveness, sustainability
The Italian Blood System
Essential figures 2012 – I

Donors: 1,739,712
Male: 69.5%
Female: 30.5%
Repeat: 1,443,770 (83%)
First-time: 295,942 (17%)
“Frequent”*: 666,479 (38% of repeat donors)
Apheresis donors: 240,218 (13.8% of total)
Apheresis-only donors: 111,312 (46.3% of apheresis donors)

Total donations: 3,191,026
/ 1,000 pop: 53.7‰

Whole blood (84%): 2,681,004
/ 1,000 pop: 45‰

Apheresis (16%): 510,022
[Plasmapheresis: 403,554]
/ 1,000 pop: 8.6‰

Donations / donor / year : 1.83

* National definition: donating at least once a year, every year, in the last 5 years
## Overview on the Italian Blood Transfusion System

### The Italian Blood System

#### Essential figures 2012 – II

<table>
<thead>
<tr>
<th>Blood components produced</th>
<th>Blood components transfused</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Red blood cells</strong> (units): 2,666,726</td>
<td><strong>Red blood cells</strong> (units): 2,529,803</td>
</tr>
<tr>
<td>Units / 1,000 pop: 44.9 ‰</td>
<td>Units / 1,000 pop: 42.6 ‰</td>
</tr>
<tr>
<td>(30% leukodepleted)</td>
<td>(29.9% leukodepleted)</td>
</tr>
<tr>
<td><strong>Platelets</strong> (units*): 276,219</td>
<td><strong>Platelets</strong> (units*): 219,785</td>
</tr>
<tr>
<td>Units / 1,000 pop: 4.6 ‰</td>
<td>Units / 1,000 pop: 3.7 ‰</td>
</tr>
<tr>
<td>(30% apheresis)</td>
<td>(33.4% apheresis)</td>
</tr>
<tr>
<td><strong>Plasma</strong> (units**): 3,123,781</td>
<td><strong>FFP</strong> (units**): 432,884</td>
</tr>
<tr>
<td>Units / 1,000 pop: 52.6 ‰</td>
<td>Units / 1,000 pop: 7.3 ‰</td>
</tr>
<tr>
<td>[plasma for fractionation: 768,435 liters]</td>
<td>(113.218 pharmaceutical pathogen-inactivated)</td>
</tr>
<tr>
<td><strong>Others</strong> (including by-products): 1,157,683</td>
<td><strong>Total</strong>: 3,182,472</td>
</tr>
<tr>
<td><strong>Total</strong>: 7,224,409</td>
<td>Units / 1,000 pop: 53.6 ‰</td>
</tr>
</tbody>
</table>

* Adult therapeutic dose
** Recovered and apheresis

### Transfused patients

- 650,516 / year
- 1,782 patients / day
- 11 persons / 1,000 pop / year

**Average number blood components transfused per patient: 4.9**
Overview on the Italian Blood Transfusion System

RBC consumption in Europe – 2010
European Directorate for the Quality of Medicines and Healthcare (EDQM)
Council of Europe
November 2012

<table>
<thead>
<tr>
<th>Country</th>
<th>RBC / 1,000 pop</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ireland</td>
<td>30.6</td>
</tr>
<tr>
<td>Netherlands</td>
<td>32.9</td>
</tr>
<tr>
<td>UK</td>
<td>35</td>
</tr>
<tr>
<td>Spain</td>
<td>35.2</td>
</tr>
<tr>
<td>France</td>
<td>36.6</td>
</tr>
<tr>
<td>Switzerland</td>
<td>39.6</td>
</tr>
<tr>
<td>Italy</td>
<td>41.8</td>
</tr>
<tr>
<td>Belgium</td>
<td>47.6</td>
</tr>
<tr>
<td>Sweden</td>
<td>51.9</td>
</tr>
<tr>
<td>Denmark</td>
<td>57</td>
</tr>
<tr>
<td>Germany</td>
<td>57.4</td>
</tr>
<tr>
<td>Greece</td>
<td>58.6</td>
</tr>
</tbody>
</table>
Overview on the Italian Blood Transfusion System

Global Red Cell Utilization Rates: 2008-09

Source: D Devine et al.: International Forum/Inventory Management, Vox Sanguinis 2009

www.AmericasBlood.org ★ 1-888-USBLOOD
Overview on the Italian Blood Transfusion System

Reasons for moving toward a patient-centric paradigm of clinical transfusion medicine practice

Eleftherios C. Vamvakas

Transfusion - 2012

PBM identifies a patient at risk of transfusion and formulates a multidisciplinary and multimodal—yet individualized—plan for reducing the need for allogeneic transfusion.

PATIENT BLOOD MANAGEMENT
Overview on:

1) Founding principles, strategic goals and essential figures of the Italian blood system

2) Italian policies for blood and blood product self-sufficiency

3) Italian policies for blood and blood product quality and safety
According to the “New discipline of blood transfusion activities and national production of plasma-derived medicines” (Law of 21 October 2005, n. 219, article 14), a national self-sufficiency program must be issued by the Ministry of Health every year.

Annual technical proposals for this program must be provided for by the National Blood Centre (NBC) after consultation with the relevant stakeholders (Regional Blood Centres and Blood Donor Associations).

The annual self-sufficiency program includes prescriptions, recommendations and objectives both on blood and blood product demand and use and on blood and blood component collection and plasma for fractionation production.
SELF-SUFFICIENCY IN SAFE BLOOD AND BLOOD PRODUCTS IN ITALY

Annual national program for blood and blood product self-sufficiency

*A thoroughly web-based process*
Annual national program for blood and blood product self-sufficiency

*Formally adopted – Official Journal of the Italian Republic*

**SERIE GENERALE**

**GAZZETTA UFFICIALE**

DECRETO 11 aprile 2008.


Programma per l’autosufficienza nazionale del sangue e dei suoi prodotti per l’anno 2009.

Programma di autosufficienza nazionale del sangue e dei suoi prodotti per l’anno 2010.

Programma di autosufficienza nazionale del sangue e dei suoi prodotti per l’anno 2011.

Programma di autosufficienza nazionale del sangue e dei suoi prodotti per l’anno 2012.

**PROGRAMMA di AUTOSUFFICIENZA NAZIONALE DEL SANGUE E DEI SUOI PRODOTTI ANNO 2013**
SELF-SUFFICIENCY IN SAFE BLOOD AND BLOOD PRODUCTS IN ITALY

Annual national program for blood and blood product self-sufficiency

Quantitative objectives

DRIVING PRODUCTS
- RED BLOOD CELLS
- PLASMA FOR FRACTIONATION

DRIVING ACTION
- RECRUITMENT OF NEW VNR BLOOD DONORS

QUANTITATIVE OBJECTIVES

PLANNING (regional and national level):
- RBC production
- RBC consumption (transfused + discarded)
- RBC discard (expiry, product defect, donor deferral)
- RBC supply to non self-sufficient Regions
- RBC supply to other Countries, when applicable
- PLASMA for fractionation production
- NEW DONORS recruitment

INDICATORS (KPIs)

3.3.2 Indicators
3.3.2.1 Ai fini del monitoraggio dell’autosufficienza, nonché di garantire un adeguato funzionamento delle monopoli e dei centri di approvvigionamento nazionale:
- n. unità di GR prodotte
- n. unità di GR consumate
- n. unità di GR eliminate
- indice n. unità di GR prodotte / 1.000 pop
- indice n. unità di GR consumate / 1.000 pop
- indice n. unità di GR trasfuse / 1.000 pop
- Kg di plasma inviati alla lavorazione industriale
- Kg di plasma inviati alla lavorazione industriale / 1.000 pop
- indici di appropriaitezza della programmazione della produzione e dei consumi rispetto ai dati consuntivi di produzione e consumo.
SELF-SUFFICIENCY IN SAFE BLOOD AND BLOOD PRODUCTS IN ITALY

Annual national program for blood and blood product self-sufficiency

Qualitative objectives, monitoring indicators, recommendations

QUALITATIVE OBJECTIVES

- Maintain VNRBD
- Blood donor management effectiveness
- Reduce first-time donors / donations
- TTIs special programs
- Enhance GP/GMP compliance
- Plasma Master File
- Patient blood management
- R & D

Monitoraggio dell’andamento dei seguenti indicatori:
- n. donatori "first time" (occasionali) / n. donatori totali;
- n. nuovi donatori sottoposti a screening e differimento della prima donazione / n. totale nuovi donatori;
- n. nuovi donatori sottoposti a screening per differimento della prima donazione che effettuano nell’anno di riferimento il loro primo ulteriore dono sottoposto a screening;
- indici di performance delle malattie infettive trasmissibili con la trasfusione (HBV, HCV, HIV), stratificati secondo quanto previsto dal programma nazionale di sorveglianza gestito attraverso il Sistema informativo nazionale dei servizi trasfusionali (SISTRA).

RECOMMENDATIONS

Raccomandazioni:
- Con riferimento ai percorsi diagnostico-terapeutici medici e chirurgici a maggiore impatto trasfusionale, si raccomanda di definire e promuovere l’applicazione di approcci multidisciplinari evidence-based, finiti le procedure e i criteri che esprimerebbero l’obiettivo di ridurre o eliminare il numero di donazioni di eccesso di emoglobina, l’ottimizzazione dell’emostasi e la minimizzazione delle perdite ematiche. In tali ambiti, identificare i pazienti a rischio di trasfusione e definire piani di gestione clinica dello stesso ("patient blood management") tesi a ridurre o eliminare il bisogno di trasfusione allogenica, riducendo al contempo i rischi ed i costi ad essa collegati.
SELF-SUFFICIENCY IN SAFE BLOOD AND BLOOD PRODUCTS IN ITALY

Annual national program for blood and blood product self-sufficiency

*Monitoring the appropriateness of planning*

**GREEN** = result / planned ±1%

**RED** = result / planned < -1%

**BLUE** = result / planned > +1%

Nationally: result / planned ±1%
SELF-SUFFICIENCY IN SAFE BLOOD AND BLOOD PRODUCTS IN ITALY

Annual national program for blood and blood product self-sufficiency
Planned inter-regional supply to non self-sufficient Regions

RBC production
Units /1,000 pop

RBC consumption
Units / 1,000 pop

ITALY: 44.5‰

ITALY: 42.2 ‰

Blue line: NON self-sufficient Region
Balancing demand and supply **out of planned** RBC exchange

National blood electronic board

Also requests for specific / “rare” BC phenotypes
National blood electronic board

**Daily (12 AM) email notification**

Availability / Shortage

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**DISPONIBILITA' NAZIONALE DI EMOCOMPONENTI - 03/05/2013 Ore 12:00**

<table>
<thead>
<tr>
<th>Emocomponente</th>
<th>Totale</th>
<th>Regioni</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emarie concentrate</td>
<td></td>
<td>Lombardia: 2914 (0+ 1200, AB- 6, B- 13, B+ 195, AB+ 105, A+)</td>
</tr>
<tr>
<td>private del buffy-coat risposte</td>
<td>3717</td>
<td>Marche: 250 (0+)</td>
</tr>
<tr>
<td>in soluzioni additive</td>
<td></td>
<td>Campania: 469 (0+ 80, B- 14, B+ 140, AB+ 10, A)</td>
</tr>
<tr>
<td>Emarie concentrate leucodeplete pre-</td>
<td></td>
<td>Puglia: 84 (0+ 40, B+ 20, A)</td>
</tr>
<tr>
<td>storage</td>
<td>707</td>
<td></td>
</tr>
</tbody>
</table>

Da: SISTRA@sanita.it [SISTRA@sanita.it]
Inviato: venerdì 3 maggio 2013 12.00
Oggetto: BACHECA NAZIONALE - Avvisi
Research related to self-sufficiency and appropriateness

PLASMA-DERIVED MEDICINAL PRODUCTS (PDMP)

Analysis of the demand for the main plasma-derived medicinal products in Italy 2007-2011

December 2012

http://www.iss.it/binary/publ/cont/dodici53web.pdf
Plasma-derived medicinal products: demand and clinical use

Guest editors

Giuliano Grazzini & Pier Mannuccio Mannucci

September 2013

http://www.simti.it - From 15th October 2013
Free download
Overview on:

1) Founding principles, strategic goals and essential figures of the Italian blood system

2) Italian policies for blood and blood product self-sufficiency

3) Italian policies for blood and blood product quality and safety
Transfusion safety is more than component safety. Safe transfusion therapy depends upon an interconnected series of processes that begin with the donor and end with the patient (Dzick WH, Transfusion 2003).
And ... quality and safety of plasma for fractionation shall be guaranteed, according to European regulatory provisions.
2.2.1 Compliance with European Pharmacopoeia Monographs.

Confirm compliance with the Ph. Eur. Monograph for Human Plasma for Fractionation and with any requirements for particular products for which Ph. Eur. Monographs exist. Describe the conditions for processing including freezing, and for storage of plasma for every establishment or centre responsible for collecting blood/plasma. Compliance with the Ph. Eur. requirements for freezing and storage should be included in Annex II, with an indication of whether requirements for recovery of proteins that are labile or not labile in plasma are met. Confirm validation of the freezing conditions.
Policies for blood and blood product quality and safety shall comply with national and European regulations in force.

- **First transposition**

- **Transposition**
  - Directive 2006/86/EC [January 2010]
  - Directive 2006/16/EC [January 2010]

- **Transposition**
  - Directive 2005/61/EC
  - Directive 2001/83/EC

- **EMA / GMP Guidelines**
  - 2006 - 2011

- **MEDICINAL PRODUCTS**

- **CELLS**

- **TISSUES**

- **BLOOD**

- **Good Practice + Good Manufacturing Practice**
  - Consistent Quality
Blood safety is best guaranteed by an appropriate quality system management

NO QUALITY, NO SAFETY
BLOOD AND BLOOD PRODUCT SAFETY

TO WHAT EXTENT?
BLOOD AND BLOOD PRODUCT SAFETY

A.L.A.R.A.
As Low As Reasonably Acceptable RISK

versus

SAFETY «AT ANY COST»
Risk-based approach for blood safety
Risk-based approach for blood safety

1. A comprehensive approach to blood safety requires the development of an integrated risk management framework that encompasses ‘vein to vein’, and beyond.
2. Decision-making based on transparent principles of risk management.
3. A system that balances risks, costs and benefits in a sustainable manner.
4. Meaningful engagement with interested and affected parties throughout the process of risk decision-making.
5. Adherence to well-established ethical principles, including autonomy, beneficence, non-maleficence and justice to ensure that the rights of both donors and recipients are respected.

The 5 dimensions of a risk-based approach for blood safety
Cooperating parties for blood safety in Italy

- National Institute of Health
- Regional Health Authorities
- Hospitals
- National Blood Centre
- Regional Blood Centres
- Scientific Societies
- Blood Establishments
- Blood Donors Associations
- Ministry of Health
- Regional Health Authorities
- Health economics advisors
- and others
1. **Analyze actual safety “coverage” of blood and blood products according to:**
   - national and European regulation
   - systematic evidence-based scientific update / progress
   - epidemiological evidence (including continuous monitoring emerging and re-emerging pathogens, haemovigilance data, etc.)
   - systematic collaboration with regulatory / international bodies / networks (EC, EDQM, ECDC, CDC, Haemovigilance Systems, etc.)
   - Specific / emerging needs / issues

2. **Adopt risk-based approach (risk assessment) and cost-benefit criteria,** reasonably balanced with the EU precautionary principle, when applicable

3. **Realize Health Technology Assessment (HTA) studies** whenever cost-benefit / cost-utility of potential interventions result uncertain / questionable

4. **Evaluate sustainability vs. potential benefit**
1. Promotion of compliance with European regulatory provisions (Directives, applicable EMA/GMP Guidelines) concerning blood, blood components (BCs) and plasma for fractionation

2. Application of quality systems fully compliant with licensing and accreditation requirements in all blood establishments (BEs) and blood collection units (BCUs) (in place since 2010)

3. New blood inspection system (including mandatory participation of nationally qualified assessors in regional inspection teams) envisaging on-site inspections of BEs and BCUs every two years (in place since 2010)


5. New national mandatory standards for blood donor selection, blood and BC collection, testing, storage, issuing, distribution, transfusion, including further BC safety and standardization requirements (coming into force end 2013)
6. New national mandatory procedures to ensure transfused patients’ safety - bedside *(coming into force end 2013)*


8. NBC institutional External Quality Assessment (EQA) scheme on serological and NAT blood testing *(in place since 2009)*

9. NBC HTA studies: 2 HTA studies on pathogen inactivation of i) platelets and ii) fresh frozen plasma *(in progress – results expected by May 2014)*

10. National guidelines for the appropriate and safe clinical utilization and management of blood components *(Patient Blood Management (PBM) national project: started July 2013).*
## Policies / interventions for quality and safety

<table>
<thead>
<tr>
<th>Blood donor selection</th>
<th>Mandatory blood testing</th>
<th>Mandatory blood component requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk-based approach</strong>&lt;br&gt;Applied to donors from Italian regions and foreign countries where prevalence/incidence of TTIs is higher than national averages</td>
<td><strong>Serology</strong>&lt;br&gt;• HBsAg, Anti-HCV, Anti-HIV1-2 + HIV1-2Ag (combo test), Syphilis</td>
<td><strong>Red blood cell and platelet pre-storage leukodepletion</strong>&lt;br&gt;• at present: 35%&lt;br&gt;• by 2014: 100%</td>
</tr>
<tr>
<td><strong>Only transfusion medicine physicians or suitably trained physicians</strong> (no other healthcare professionals!) are allowed to assess donors’ eligibility</td>
<td><strong>NAT</strong>&lt;br&gt;• HBV, HCV, HIV1&lt;br&gt;• WNV (1(^{\text{st}}) July – 30(^{\text{th}}) November, in areas selected according to risk assessment and EU preparedness plan)</td>
<td><strong>Fresh frozen plasma</strong>&lt;br&gt;• male-only plasma for transfusion&lt;br&gt;• pathogen inactivation not mandatory so far</td>
</tr>
<tr>
<td><strong>Blood donor pre-qualification</strong> (blood donor testing before first donation)&lt;br&gt;• applied voluntarily in most Italian northern Regions&lt;br&gt;• under preliminary investigation / impact evaluation (maybe in cooperation with ECDC) for national mandatory application&lt;br&gt;• national workshop scheduled February 2014</td>
<td><strong>Immunohaematology</strong>&lt;br&gt;<strong>New donors</strong>: full ABO and Rh (CcDEe) typing, Kell typing, Indirect antiglobulin test (IAT)&lt;br&gt;• full Rh and Kell phenotype to be confirmed at 2(^{\text{nd}}) donation&lt;br&gt;<strong>Repeat donors</strong>: from 3(^{\text{rd}}) donation: ABO and RhD control, IAT if potentially immunizing event (pregnancy, red cell transfusion)</td>
<td><strong>BC pathogen inactivation ?</strong>&lt;br&gt;• 2 full HTA (Health Technology Assessments) studies on FFP and PLT ongoing (should be published by June 2014)&lt;br&gt;• 1 randomized controlled trial (IPTAS) on PLT pathogen inactivation ending June 2014&lt;br&gt;• policies to be decided according to HTAs and RCT results</td>
</tr>
</tbody>
</table>
### Policies / interventions for quality and safety

<table>
<thead>
<tr>
<th>Quality system requirements and inspections</th>
<th>Appropriate management and clinical use of blood components</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quality system requirements</strong>&lt;br&gt;National requirements complying with European directives (including EU GMPs pertaining to plasma for fractionation)</td>
<td><strong>Management</strong>&lt;br&gt;According to GPs and annual national Program for self-sufficiency (prevention of BC expiry, adequate stock management and turn-over, etc.)</td>
</tr>
<tr>
<td><strong>Inspections</strong>&lt;br&gt;Performed by regional health authorities (inspection teams must include at least 1 nationally qualified inspector) every 2 years</td>
<td><strong>Clinical use</strong>&lt;br&gt;- by law transfusion medicine physicians <strong>must</strong> assess the clinical appropriateness of transfusion requests and provide counseling to prescribing colleagues&lt;br&gt;- drastic reduction (&quot;sunset&quot;) of autologous transfusion&lt;br&gt;- role of hospital transfusion committees&lt;br&gt;- <strong>national Patient Blood Management program</strong> just launched - July 2013 - (+ participation of Italy in EU tender for a project aimed at producing a EU PBM Guide)</td>
</tr>
<tr>
<td><strong>Regional health authorities</strong> are the competent authorities for <strong>Licensing and Accreditation</strong> procedures</td>
<td></td>
</tr>
</tbody>
</table>
The National Haemovigilance System

Main policies / interventions for quality and safety

- TTIs surveillance
- SARs in blood donors
- SARs in transfused patients and human errors
- SAEs throughout the transfusion process

Haemovigilance fields
Blood Transfusion Centres

Regional Blood Centres

National Blood Centre

International networks

THE NATIONAL BLOOD INFORMATION SYSTEM

Notifications

Single notification

local annual report

regional annual report

regional annual reports

Web-based system

National annual report
Policies for blood quality and safety

Final comments - 1

✓ In Italy, the overall safety of blood, BCs and transfusion medicine activities is at a good level, especially for transfusion-transmissible infections; haemovigilance and clinical risk management systems do contribute to comprehensive blood and blood product safety evolution.

✓ Notwithstanding, continuous improvement and optimization of safety strategies must be pursued, taking into account risk management approaches, cost/benefit of interventions and their overall sustainability.

✓ Full compliance with regulatory quality standards and inspection system as envisaged by EU blood directives and applicable GMPs shall be achieved nationwide by 31st December 2014.
Progress towards a scenario encompassing a homogeneous compliance with EU regulatory requirements and an effective and regular inspection system is challenging due to the lack of homogeneity and unbalanced evolution of Blood Establishments in the Italian Regions (gradient north-south) and to the delay of systematic processing and testing consolidation.

Any existing or new blood safety intervention is optimally applied within a well-established, suitably-managed, third-party-assessed quality system.

Application of guidelines/criteria for the appropriate management and clinical utilization of blood resources is of paramount importance as it represents a fundamental “parallel tool” for blood and blood product self-sufficiency, as well as a safety measure per se. National PBM policies have just been launched by the National Blood Centre & its multi-professional Partners and shall be a must for the future of clinical transfusion.
Thanks for your attention!