FUTURO
INIBITORE
IMMUNOTOLLERANZA
CURA
PERSONALIZZAZIONE
SISTEMA SANITARIO NAZIONALE
ACCESSO
ENGAGEMENT
EMOFILIA
PLASMA
EMOSTASI
DONATORI
OMEOSTASI
ERADICARE
FISIOTERAPIA
TERAPIA SOSTITUTIVA
PROFILASSI
PAZIENTE
SALUTE
FARMACOCINETICA
FATTORE VIII

27/28 GIUGNO 2019
TRIESTE
SAVOIA EXCELSIOR PALACE

EMOFILIA

LA CERTEZZA DELLA CURA

TERAPIA SOSTITUTIVA, PERSONALIZZAZIONE, ACCESSO

I Farmaci Derivati dal Plasma: La Prospettiva dell'Industria

Alessandro Gringeri, MD, M.Sc.

CHIEF MEDICAL AND RESEARCH & DEVELOPMENT OFFICER
KEDRION BIOPHARMA

A bit of history…

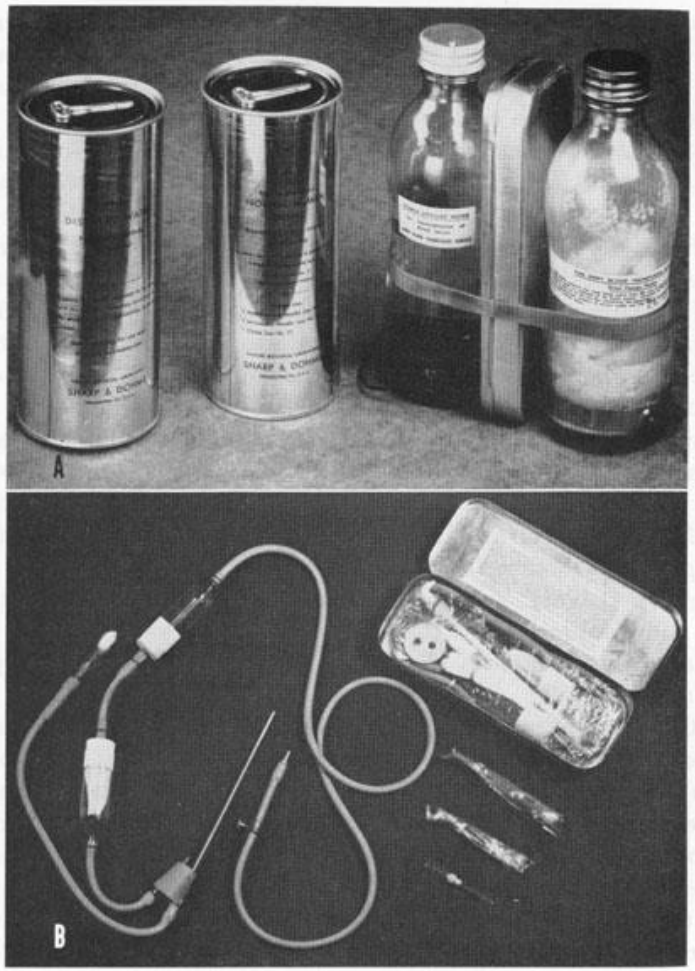


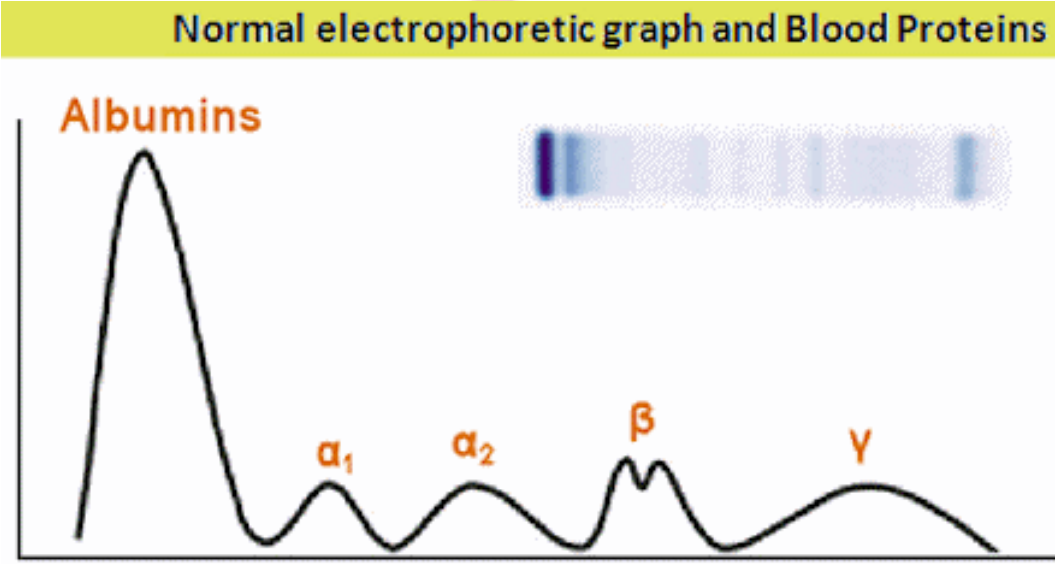
FIGURE 4.—British and Canadian materials and equipment for replacement therapy. A. British (right) and U.S. Army dried plasma units. B. British dispensing set for plasma.

Ca. 1550: Vesalius was probably the first who suggested the use of the liquid phase of blood.
1628: Plasma was first described by William Harvey
1770: discovery of fibrinogen by William Henson
1918: use of blood plasma as a substitute for whole blood was proposed in he British Medical Journal, by Gordon R. Ward
1939: liquid plasma and whole blood were used in wounded soldiers
1943: "Dried plasmas" in powder or strips of material format were developed and first used in World War II by United States' army

FIGURE 77.—Administration of blood plasma in battalion aid station, about half mile behind frontlines, S. Agata, Sicily, 9 August 1943. The same first aid station is shown in the frontispiece of this volume.

Cohn, E. J. (1948) The history of plasma fractionation. *Adv. Mil. Med.* **1,** 364–443

Plasma proteins



Blood protein	Normal level	%	Function
Albumins	3.5-5.0 g/dl	55%	create and maintain oncotic pressure; transport insoluble molecules
α1-Globulin	0.35-0.5 g/dl	5.3%	α1-Antitrypsin, TBG, Transcortin, etc
α2-Globulin	0.5-0.7 g/dl	8.6%	Haptoglobulin, ceruloplasmin, α2-macroglobulin, clotting factors, etc
β-Globulin	0.7-0.9 g/dl	13.4%	β1-transferrin, β-lipoprotein, etc
Globulins	2.0-2.5 g/dl	38%	participate in immune system

Plasma proteins for therapeutic use – 1

Plasma protein	Indications
Factor VIII	Congenital and acquired haemophilia A
Von Willebrand Factor	Congenital and acquired von Willebrand Disease
Activated Prothrombin Complex (*Factor Eight Inhibitor Bypassing Activity*)	Acquired haemophilia A
Prothrombin Complex	Vit. K antagonist reversal agent
Factor IX	Congenital and acquired haemophilia B
Fibrinogen, Prothrombin, Factor V, Factor X, Factor XI, Factor XIII	Congenital and acquired single clotting factor deficiency
Antithrombin III	Congenital and acquired ATIII deficiency
Protein C	Congenital and acquired Prot. C deficiency
Fibrin Glues	To heal wounds following surgery

NL Anderson & NG. Anderson. The Human Plasma proteome. Molecular & Cellular Proteomics 1:845–867, 2002.

Plasma proteins for therapeutic use – 2

Plasma protein	Indications
Human Serum Albumin	Liver disease, sepsis, critical care
Intravenous and sub-cutaneous Immunoglobulin G	Primary and secondary immunodeficiency. Neurological inflammatory diseases, ITP
Hyperimmune Immunoglobulin G	Anti-tetanus, anti-HBV, anti-rabies, anti-CMV, anti-VZV, anti-measles, anti-vaccinia, anti-hepatitis A, etc.
Rh (D) Immunoglobulin	Prevention of Hemolytic Disease of Newborn
$Alpha_1$-Proteinase Inhibitor	Congenital deficiency→pulmonary emphisema. Protecting role of other tissues
C1-Inhibitor	Congenital and acquired C1q-inhibitor deficiency
Solvent/Detergent Plasma	All plasma substitution indications

NL Anderson & NG. Anderson. The Human Plasma proteome. Molecular & Cellular Proteomics 1:845–867, 2002.

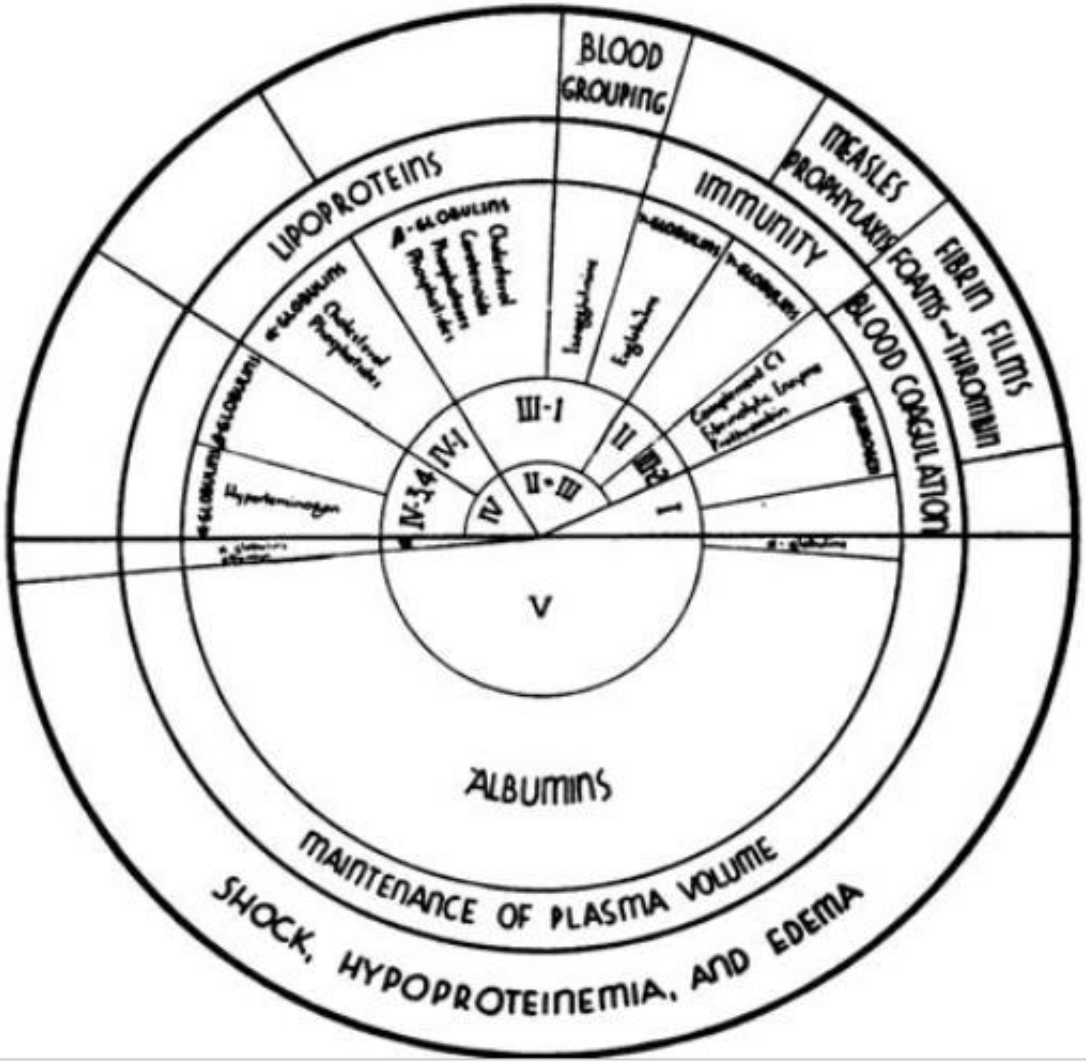
Other proteins of potential interest

Plasma protein	Potential indications
Transthyretin (TTR)	TTR misfolding and aggregation is known to be associated with the amyloid diseases senile systemic amyloidosis (SSA), familial amyloid polyneuropathy (FAP) and familial amyloid cardiomyopathy (FAC).
ADAMTS-13	Thrombotic Thrombocytopenic Purpura (TTP)
Plasminogen	Congenital and acquired plasminogen deficiency
Ceruloplasmin	Congenital and acquired ceruloplasmin deficiency
Alpha-2-macroglobulin	A common variant (29.5%) of alpha-2-macroglobulin leads to increased risk of Alzheimer's disease
Complement components	Congenital and acquired deficit of C2, C3 or C4
Haptoglobin	Congenital and acquired a-/hypo-haptoglubulinemia
Acid-Stabilized Plasmin	Novel Direct-Acting Thrombolytic Agent
High-Density Lipoprotein	Plasma-selective delipidation converts αHDL to preβ-like HDL, the most effective form of HDL for lipid removal from arterial plaques
Apolipoprotein AI_{Milano}	Coronary heart disease

Bertolini, Joseph, Goss, Neil, Curling.
Production of Plasma Proteins for Therapeutic Use. 2013

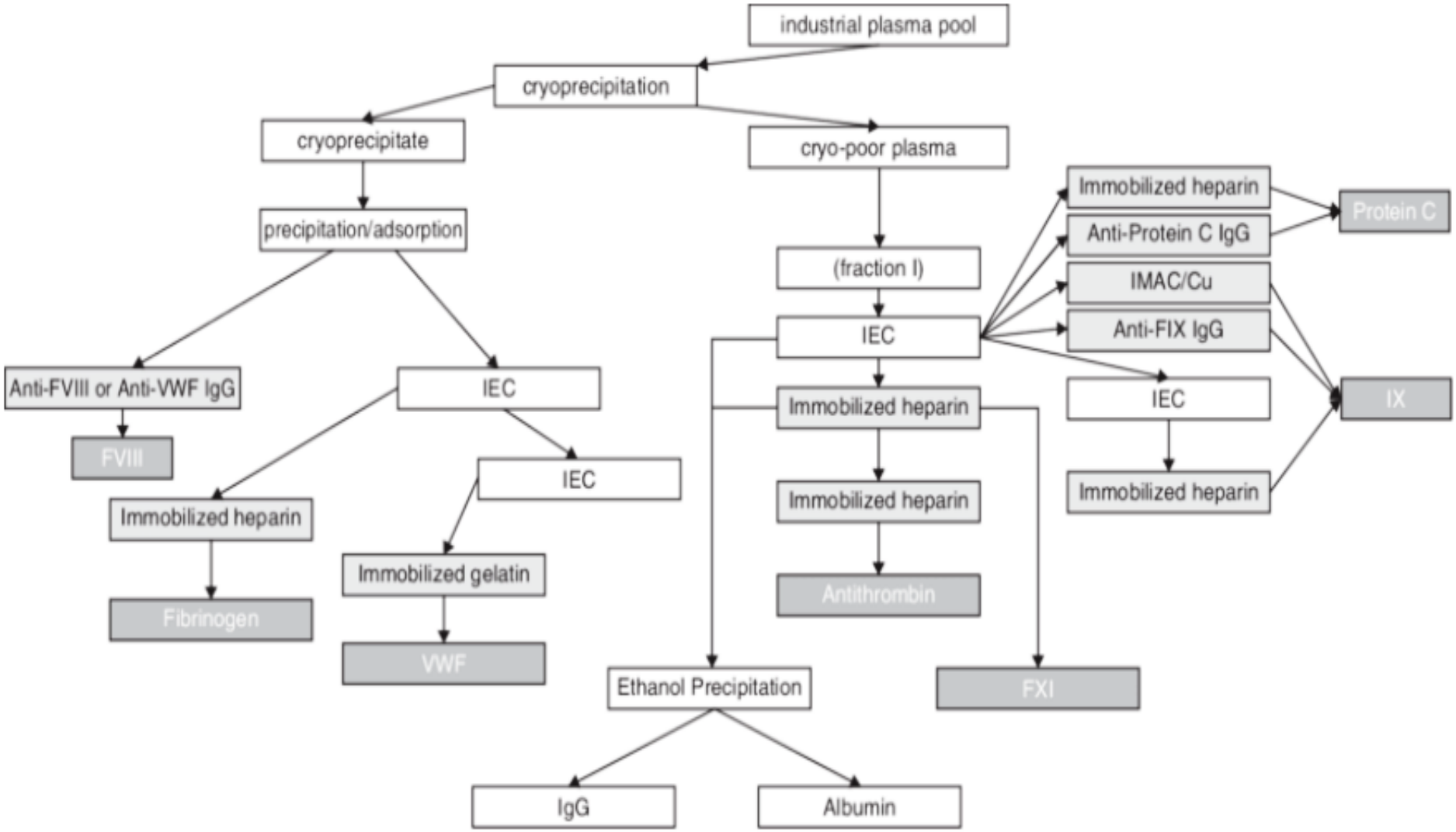
PLASMA PROTEINS

THEIR NATURAL FUNCTIONS AND CLINICAL USES AND SEPARATION INTO FRACTIONS



Cohn, E. J. (1948) The history of plasma fractionation. *Adv. Mil. Med.* **1,** 364–443

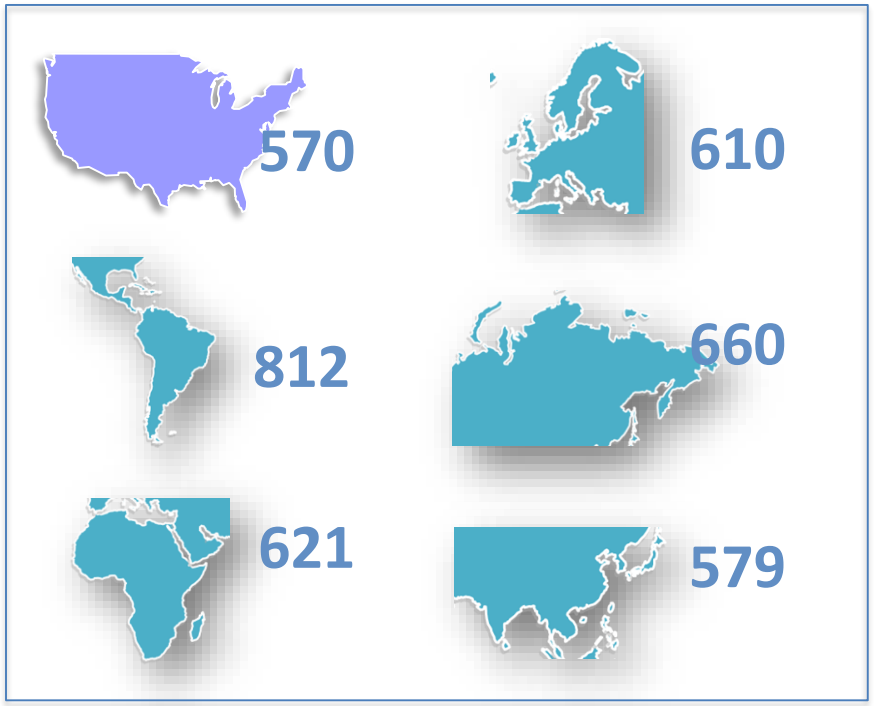
Fractionation & purification



Bertolini, Joseph, Goss, Neil, Curling.
Production of Plasma Proteins for Therapeutic Use. 2013

FVIII WORLD CONSUMPTION IN NUMBERS

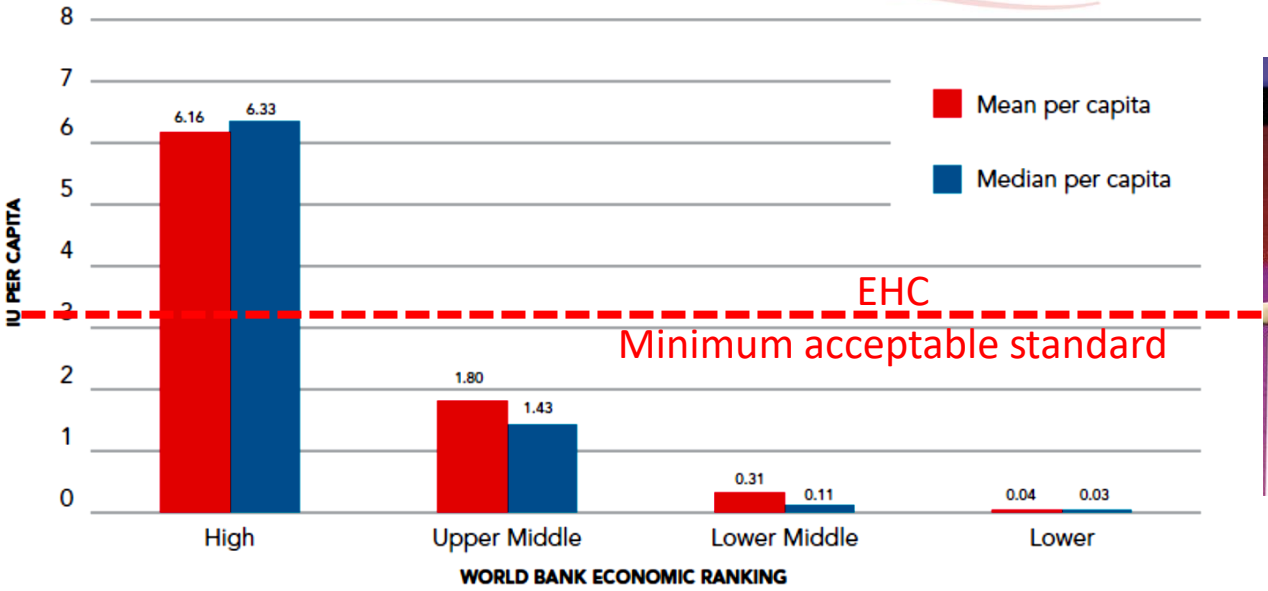
- **149,764** Patients with HA identifie
- **12,34** Billion IU Factor VIII use.
- **4,3** Billion **IU** Plasma-Derived FVI



MM IUI by Regions,

Data source : PPTA, MRB,WFH

The present status of factor VIII



"Approximately two-thirds of worldwide factor VIII supplies ***(12 billion international units per year) are used by 30%*** *of the global hemophilia A population… It would take a further* ***29 billion international units per year to provide the remaining 70% hemophilia A population*** *with the same access to treatment. "* *Alain Weill, President WFH, Glasgow May 2018*

Our vision

02 IMPROVE

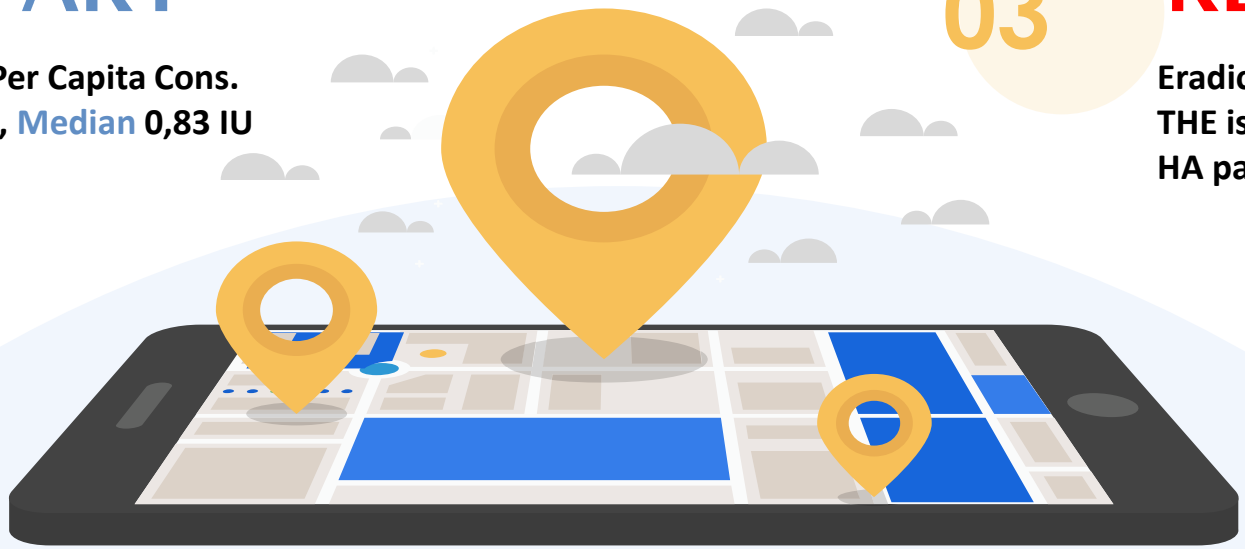
Zero bleeding- Personalization- Quality of life

01 START

FVIII WW Per Capita Cons.
Mean 2,29, Median 0,83 IU

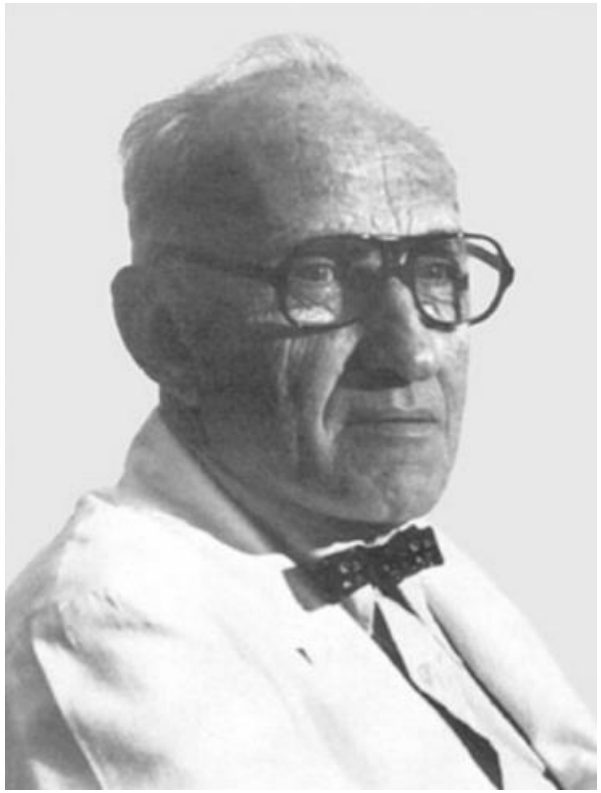
03 RESTORE

Eradicate inhibitors is THE issue for 20-30% of HA patients



«The cornerstone of hemophilia patients is represented by replacement therapy with factor VIII, which has a specific unrivalled role….» PM Manucci, EIGHT Budapest, 12 October 2018

Immunoglobulins



Elvin A. Kabat

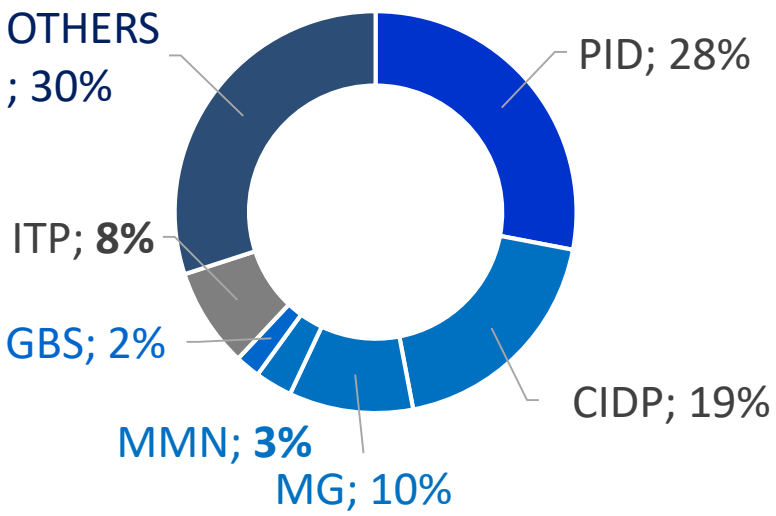
Arne Tiselius

In 1939 Kabat and Tiselius showed that antibodies belong to the γ-globulin fraction of plasma proteins

Starr, Douglas P. (2000). *Blood: An Epic History of Medicine and Commerce*. New York: Quill. ISBN 0-688-17649-6.

Medical use of Immunoglobulins and Expected Evolution in the Next Years

2018 use by disease in developed areas



Emerging economies

- IG are mainly used in PID and acute conditions.
- Medical awareness, diagnosis rate, healthcare coverage still insufficient (under development).
- SCIG adopted in a very small percentage.

- **MG:** myasthenia gravis (acute and chronic)**; ITP:** primary immune thrombocytopenia**; MMN:** multifocal motor neuropathy; **PID**: primary immundeficiences; **GBS**: Guillain Barrè; **CIDP**: chronic inflammatory demyelinating poliradiculoneuropathy.
- **Others** include secondary immunodeficiences, evidence-based / off-label treatment

Source: **MRB**, Barclays, Equita, Keplercheuvreux, companies presentations, internal assessments etc.

Medical use of Immunoglobulins and Expected Evolution in the Next Years

Evolution (next 5 years perspective)

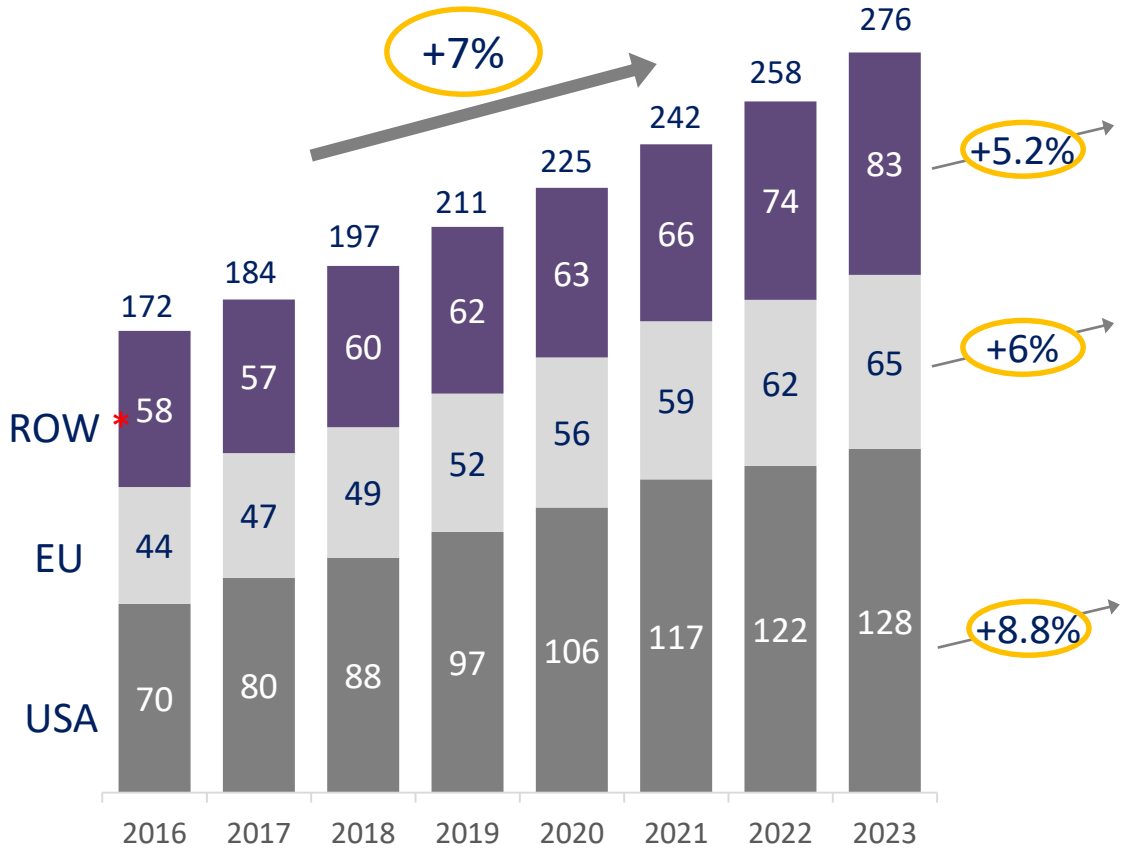
- **CIDP** will continue to grow by volume keeping the MS in IG use (primarily IVIG, increasing use of SCIG).
- **PID** will continue to grow mainly driven by SCIG.
- **ITP** estimated to decrease due to alternative treatments.
- Evidence-based / off-label demand keep continuing.
- Growing interest on **secondary immunodeficiences** (due to diseases. Immunosuppressive/oncological treatments, bone-marrow transplantation…).

- **MG:** myasthenia gravis (acute and chronic)**; ITP:** primary immune thrombocytopenia**; MMN:** multifocal motor neuropathy; **PID**: primary immundeficiences; **GBS**: Guillain Barrè; **CIDP**: chronic inflammatory demyelinating poliradiculoneuropathy.

Source: **MRB**, Barclays, Equita, Keplercheuvreux, companies presentations, internal assessments etc.

Estimated Global **IG Demand** by Geographics

WW market trend **IG** by **volume – geographic segmentation (metric tons)**



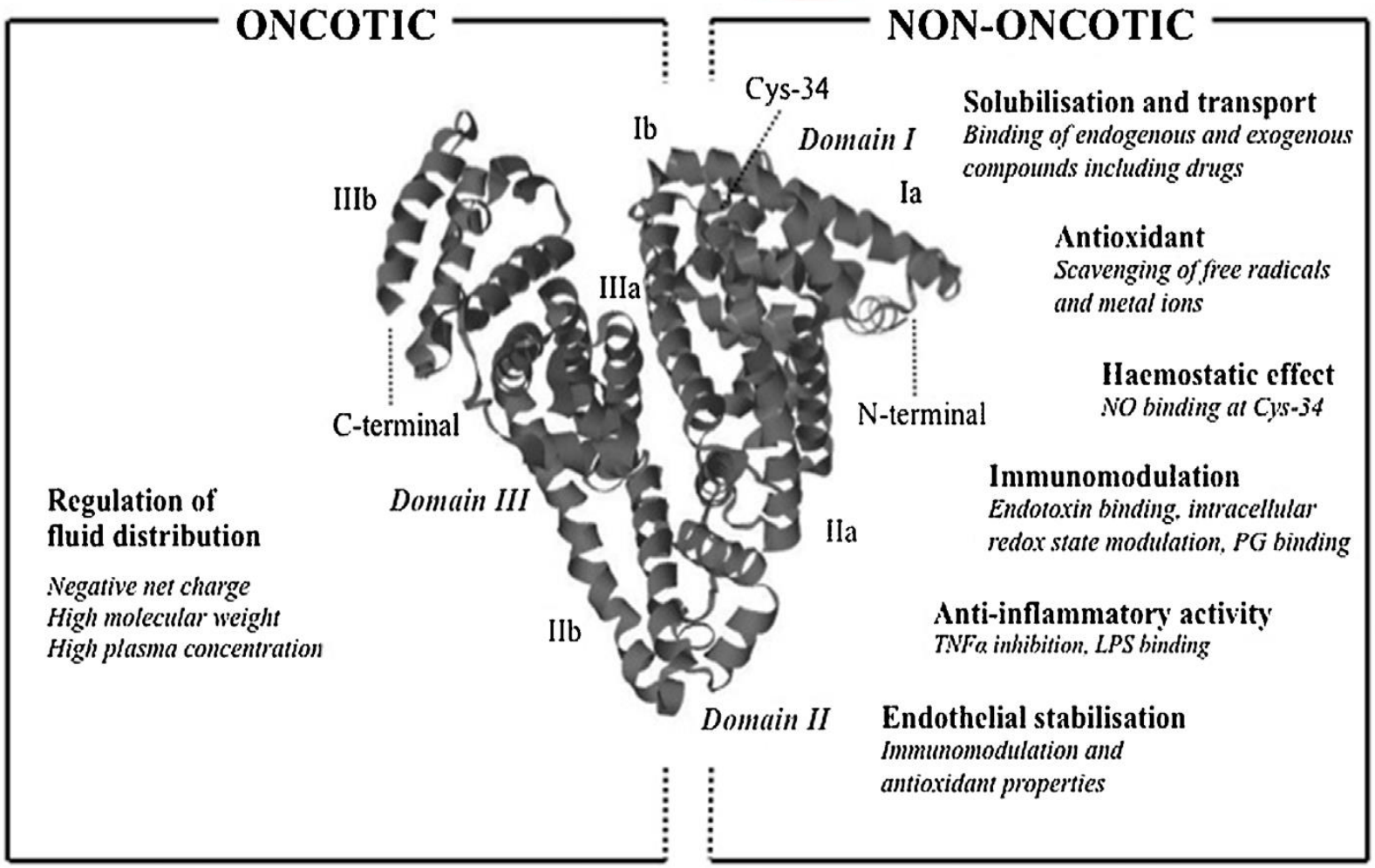
Key insights

- Global domand expected to keep growing 7-9% CAGR (7% estimated by MRB, 7-9% estimated by MST)
- USA driving by volumes and ASP, EU growing at lower rate, ROW following (based on local economies)
- Estimated challenges on IG global availability.

* ROW includes China (currently isolated market for IG)

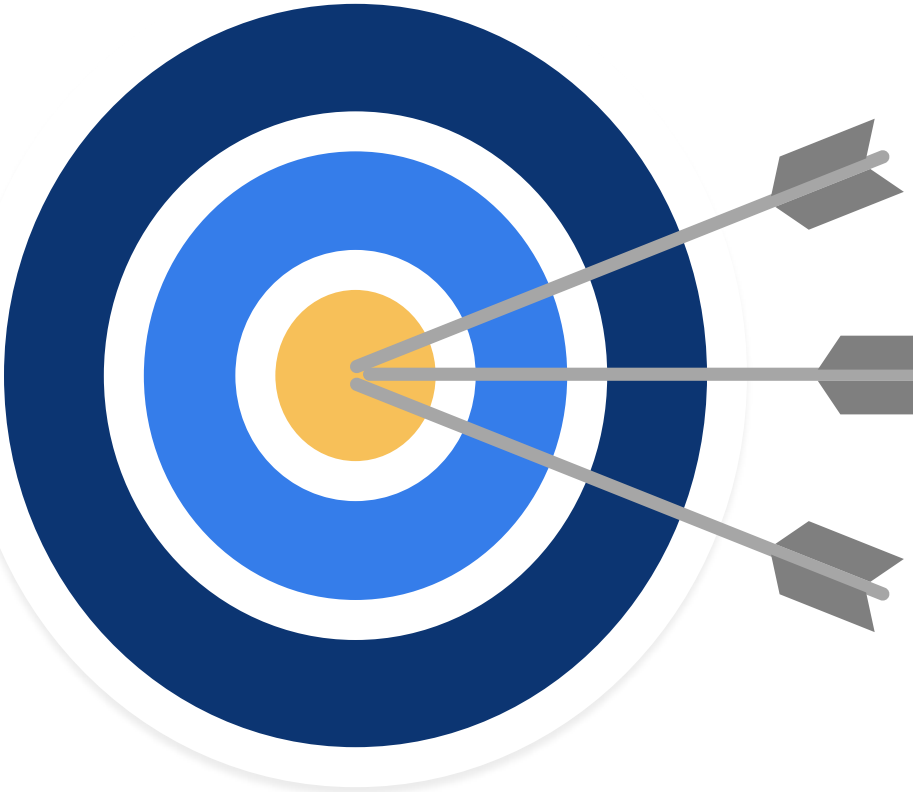
Source: MRB, PPTA, MST, internal elaboration

HUMAN ALBUMIN
THE PHYSIOLOGICAL FUNCTIONS



Italian Association for the Study of the Liver (AISF); Italian Society of Transfusion Medicine and Immunohaematology (SIMTI); Italian Association for the Study of the Liver AISF; Italian Society of Transfusion Medicine and Immunohaematology SIMTI *AISF-SIMTI Position Paper: The appropriate use of albumin in patients with liver cirrhosis.* Dig Liver Dis. 2016 Jan;48(1):4-15.

Use of albumin in clinical practice



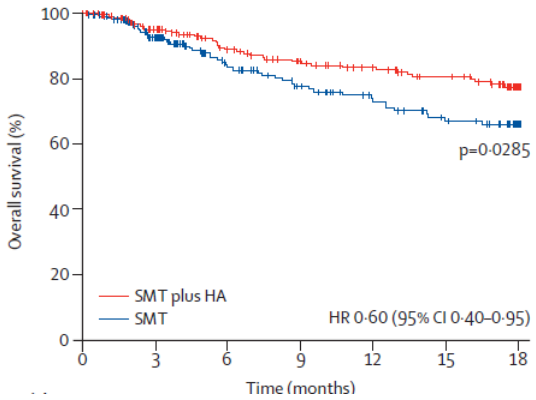
- Liver disease
- Critical care
- All conditions associated with acute reduction of effective volemia

Studio «Answer»

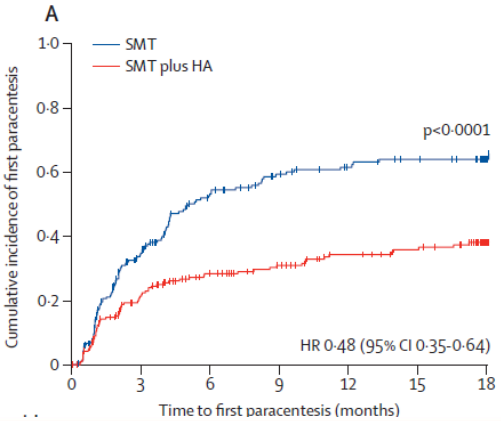
Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial

*Paolo Caraceni, Oliviero Riggio, Paolo Angeli, Carlo Alessandria, Sergio Neri, Francesco G Foschi, Fabio Levantesi, Aldo Airoldi, Sergio Boccia, Gianluca Svegliati-Baroni, Stefano Fagiuoli, Roberto G Romanelli, Raffaele Cozzolongo, Vito Di Marco, Vincenzo Sangiovanni, Filomena Morisco, Pierluigi Toniutto, Annalisa Tortora, Rosanna De Marco, Mario Angelico, Irene Cacciola, Gianfranco Elia, Alessandro Federico, Sara Massironi, Riccardo Guarisco, Alessandra Galioto, Giorgio Ballardini, Maria Rendina, Silvia Nardelli, Salvatore Piano, Chiara Elia, Loredana Prestianni, Federica Mirici Cappa, Lucia Cesarini, Loredana Simone, Chiara Pasquale, Marta Cavallin, Alida Andrealli, Federica Fidone, Matteo Ruggeri, Andrea Roncadori, Maurizio Baldassarre, Manuel Tufoni, Giacomo Zaccherini, Mauro Bernardi, for the ANSWER Study Investigators**

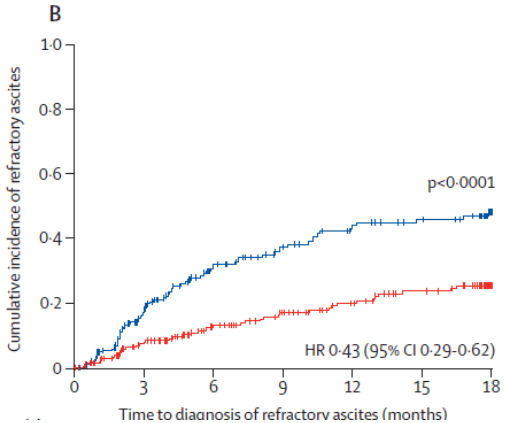
SURVIVAL



PARACENTESIS



REFRACTORY ASCITES



www.thelancet.com Published online May 31, 2018 http://dx.doi.org/10.1016/S0140-6736(18)30840-7

CONCLUSIONS

Long-term albumin administration to patients with cirrhosis and ascites:

Improves survival and the quality of life

Reduces the incidence of severe complications of cirrhosis

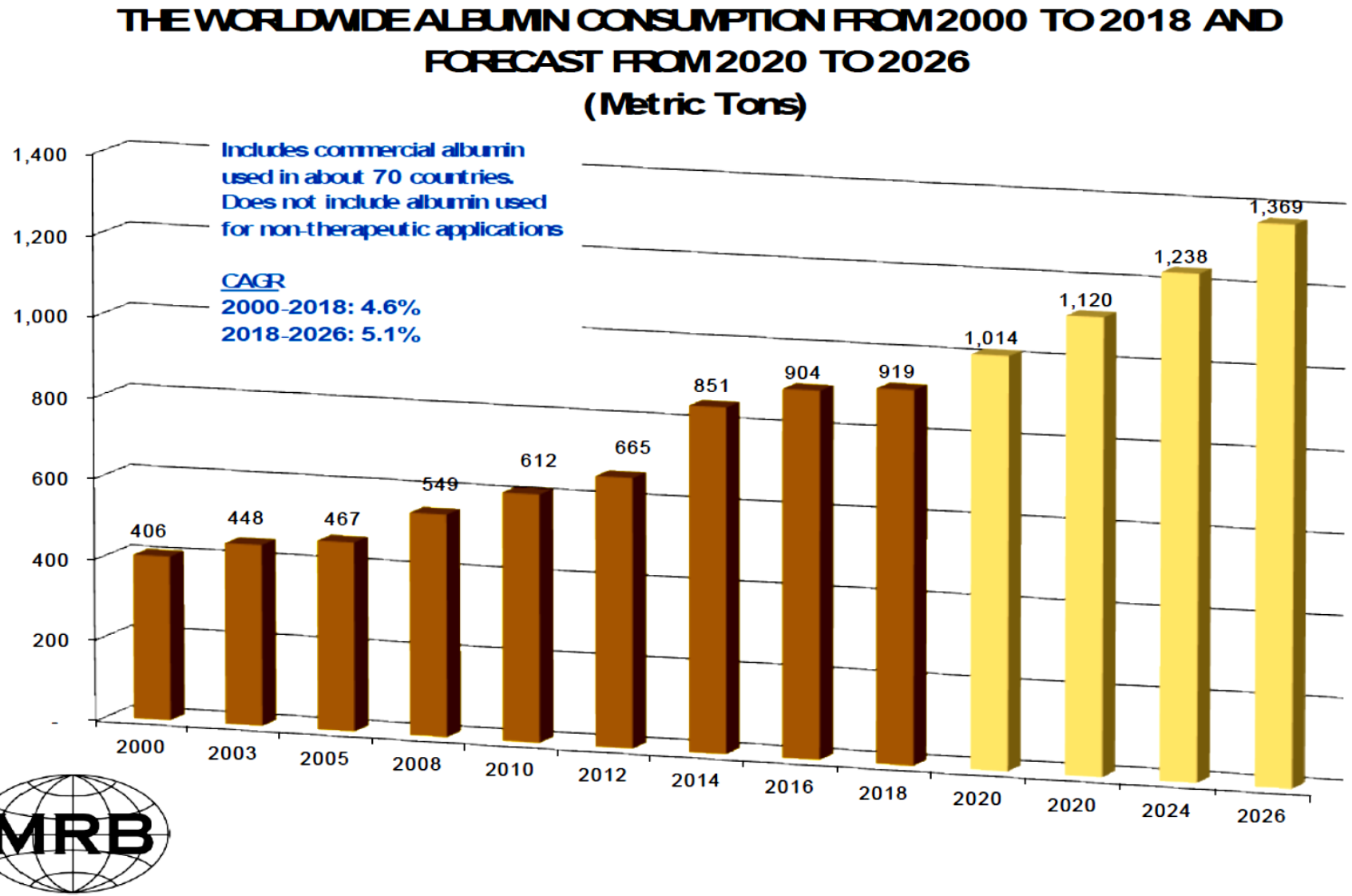
Facilitates the management of ascites

Reduces the number and duration of hospitalizations

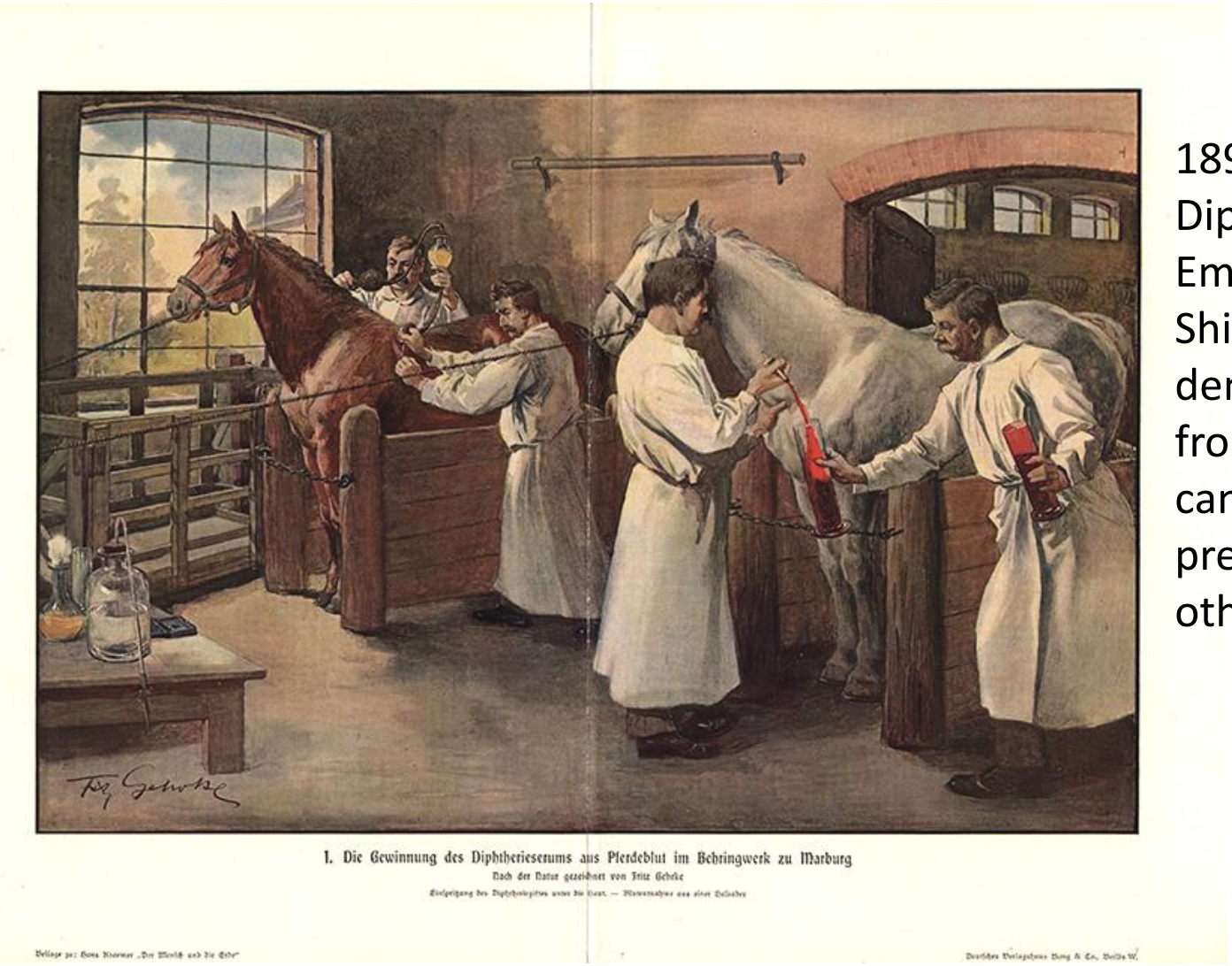
Long-term albumin administration to patients with decompensated cirrhosis could be seen as a disease-modifying treatment

www.thelancet.com Published online May 31, 2018 http://dx.doi.org/10.1016/S0140-6736(18)30840-7

ALBUMIN CONSUMPTION



Hyperimmune immunoglobulins



I. Die Gewinnung des Diphtherieserums aus Pferdeblut im Behringwerk zu Marburg

Nach der Natur gezeichnet von Fritz Gehrke

1890:
Diphtheria anti-serum: Emil von Behring and Shibasaburo Kitasato demonstrate that serum from infected animals can be used to treat and prevent infection in other animals.

Fritz Gehrke. Die Gewinnung des Diphterieserums aus Pferdeblut im Behringwerk zu Marburg. U.S. National Library of Medicine.

Rabies immunoglobulins

Rabies Ig are special neutralizing antibodies from vaccinated donors that immediately neutralize virus on contact

Rabies Ig gives a coating to the virus so that it cannot enter the nerve ending resulting in reduction or total obliteration of inoculated virus

In countries of categories I, II, and III, contacts with suspect rabid animals, including bats, should be followed by rabies post-exposure prophylaxis
High risk - Pre-exposure immunization recommended for travelers/people likely to come into contact with domestic animals, particularly dogs and other rabies vectors
Medium risk - Pre-exposure immunization recommended for travelers/people likely to come into contact with bats and other wildlife
Low risk - Pre-exposure immunization recommended for people likely to come into contact with bats
No risk - no risk at all

Anti-tetanus immunoglobulins

Opisthotonos – Charles Bell - 1809

The cause of the disease was determined in 1884 by Antonio Carle and Giorgio Rattone at the University of Turin

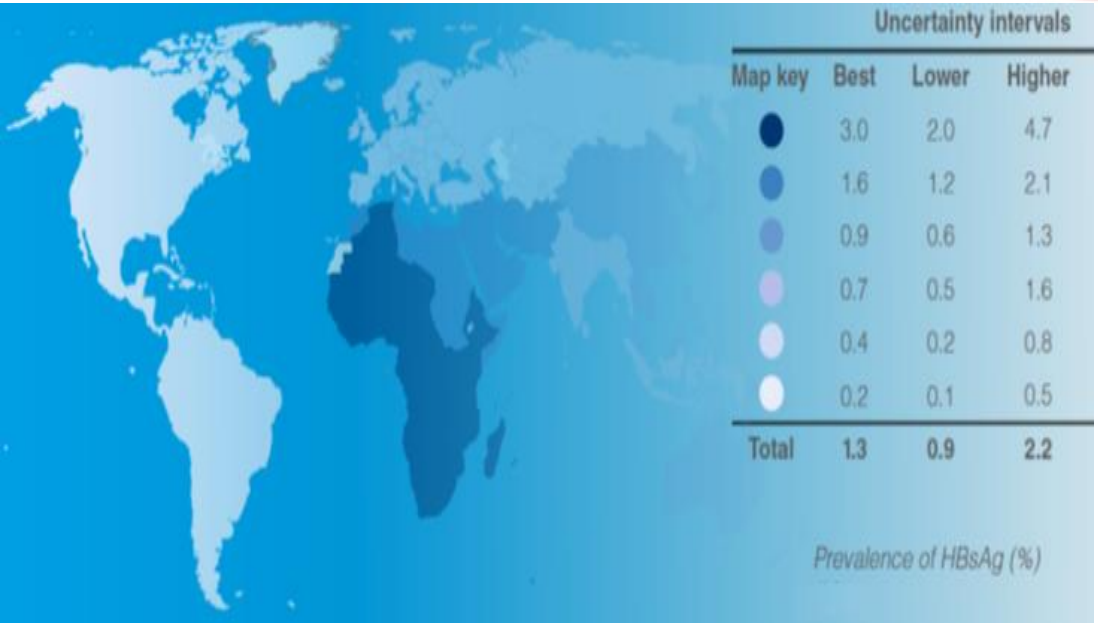
In 2015 there were about 209,000 infections and about 59,000 deaths globally.

As of 1998 neonatal tetanus was common in many developing countries and was responsible for about 14% (215,000) of all neonatal deaths.

WHO 2017 global figures on neonatal tetanus:
2'266 reported cases
61'000 estimated deaths (2011)
73% reported TT2+ coverage (among pregnant women)

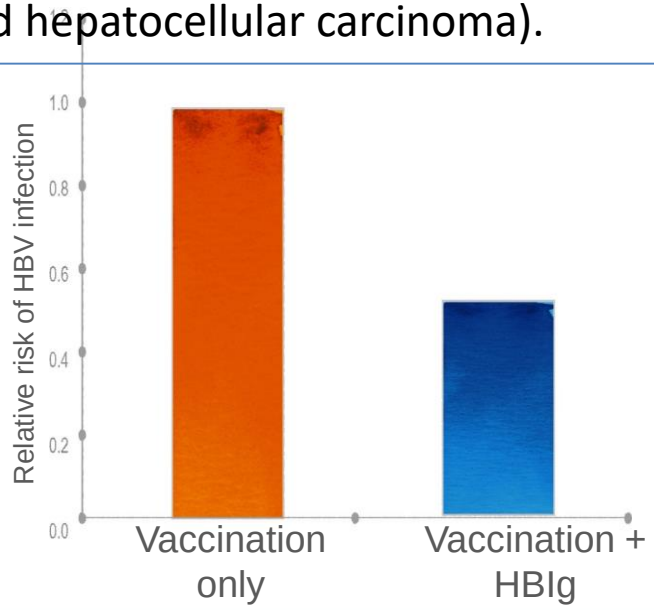
https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/neonatal_tetanus/en/
Accessed on: June 21, 2019

Hepatitis B Immunoglobulins



- ✓ Hepatitis B is a viral infection that attacks the liver and can cause both acute and chronic disease.
- ✓ An estimated 257 million people are living with hepatitis B virus infection.
- ✓ In 2015, hepatitis B resulted in 887 000 deaths, mostly from complications (including cirrhosis and hepatocellular carcinoma).

- ✓ Infants born to mothers who are positive for both HBsAg and HBeAg are at a high risk of acquiring infection (transmission risk: 70–100% in Asia and 40% in Africa)
- ✓ Early vaccination of the baby against hepatitis B with a first dose within 24 hours of birth (timely birth dose) contributes to the prevention of mother-to-child transmission but it cannot be sufficient



Source: WHO estimates, conducted by the Center for Disease Analysis.Jonas M.M.; Liver International 2009; 29 (s1): 133-139

Rh (anti-D) immunoglobulins

Hemolytic Disease of the Newborn
World figures

373.000
Cases of Rh disease

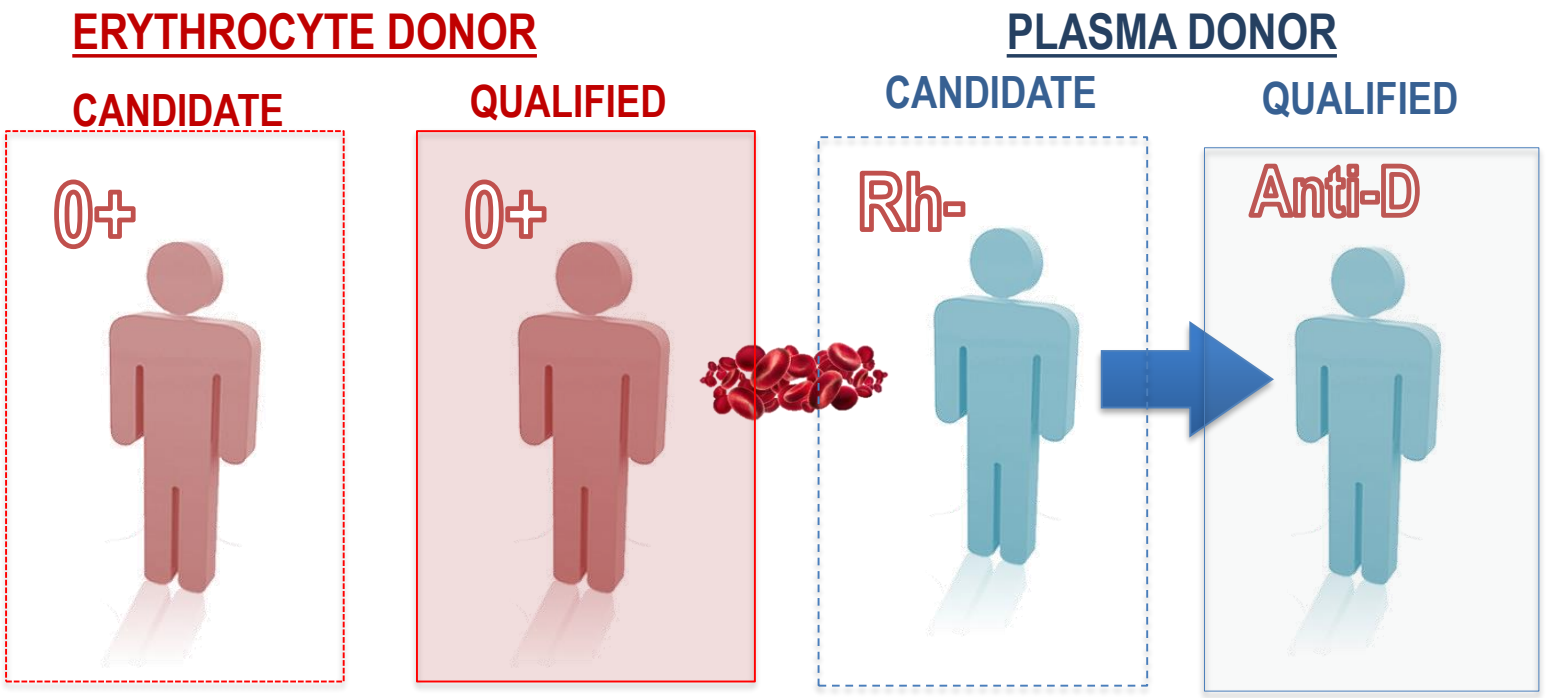
114.000
Newborn deaths

55.000
Deaths in utero

26.900
Brain damage

Neonatal hyperbilirubinemia and Rhesus disease of the newborn: incidence and impairment estimates for 2010 at regional and global levels

ANTI-D PLASMA COLLECTION AND FRACTIONATION PROCESS



LONG PROCESS, OVER 24 MONTHS,
TO OBTAIN A QUALIFIED PLASMA DONOR

50 YEARS OF ANTI-D

Guiheen L.. Oral communication. “anti D prophylaxis. An unfinished job?” IPPC Prague - 2017

CONCLUSIONS

To date, 289 proteins have been reported in plasma

Over 22 million liters of plasma are used worldwide by plasma fractionators each year to generate human therapeutic proteins.

Currently, there are more than 70 indications for plasma proteins

- ***Only a few have a recombinant alternative***

More than 1,000 studies are ongoing

Still, many proteins have to be exploited

Our Commitment

Ensure continuity of supply of raw material (plasma)

Promote research, innovation and continuous improvement of the standards of care

Enhance talent, investing on developement and growth

Promote, support and conduct disease awareness campaigns to expand access to care

Enhance our quality standards, keeping in mind our environment, energy saving and optimization

Support donors, patient associations and the scientific community in their battle to improve people's QoL