Donantes de tejidos y hepatitis B. El espejismo de lo fácil

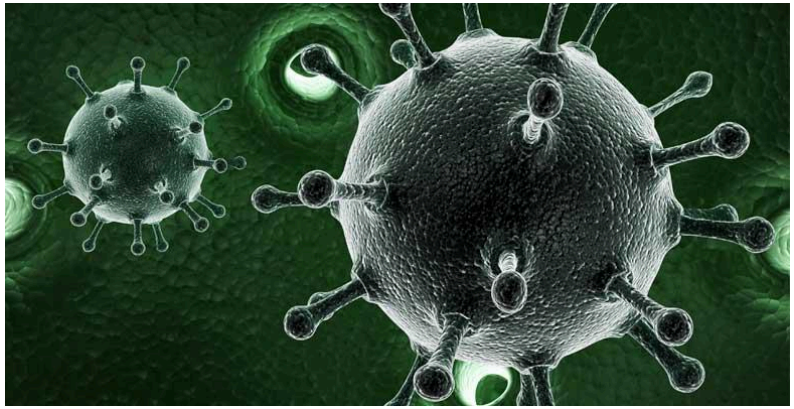
Rafael Villalba

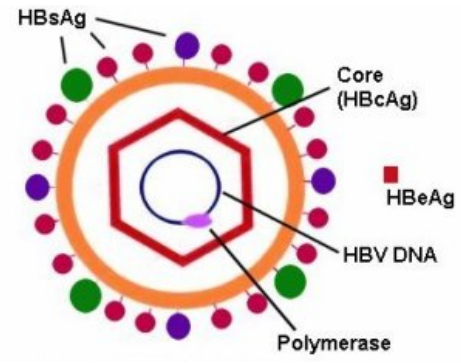
Jacinto Sánchez

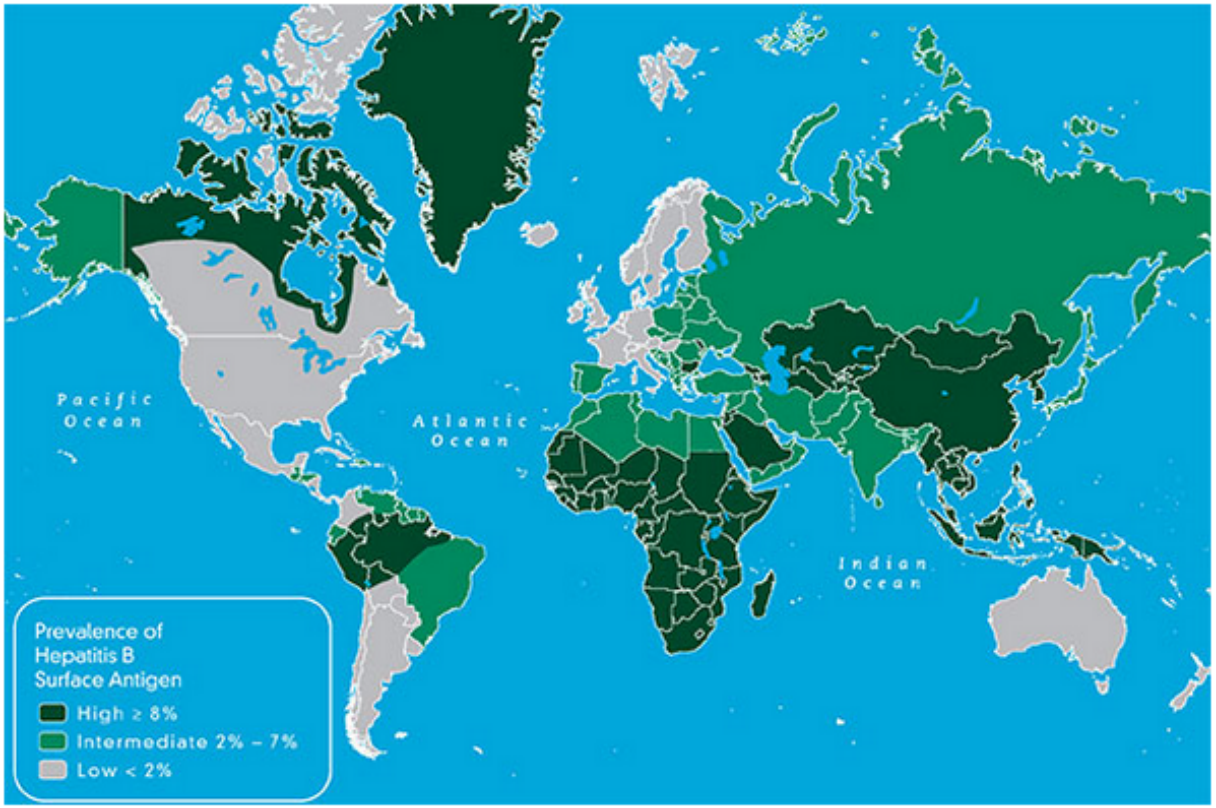
En nombre de todos los grupos colaboradores

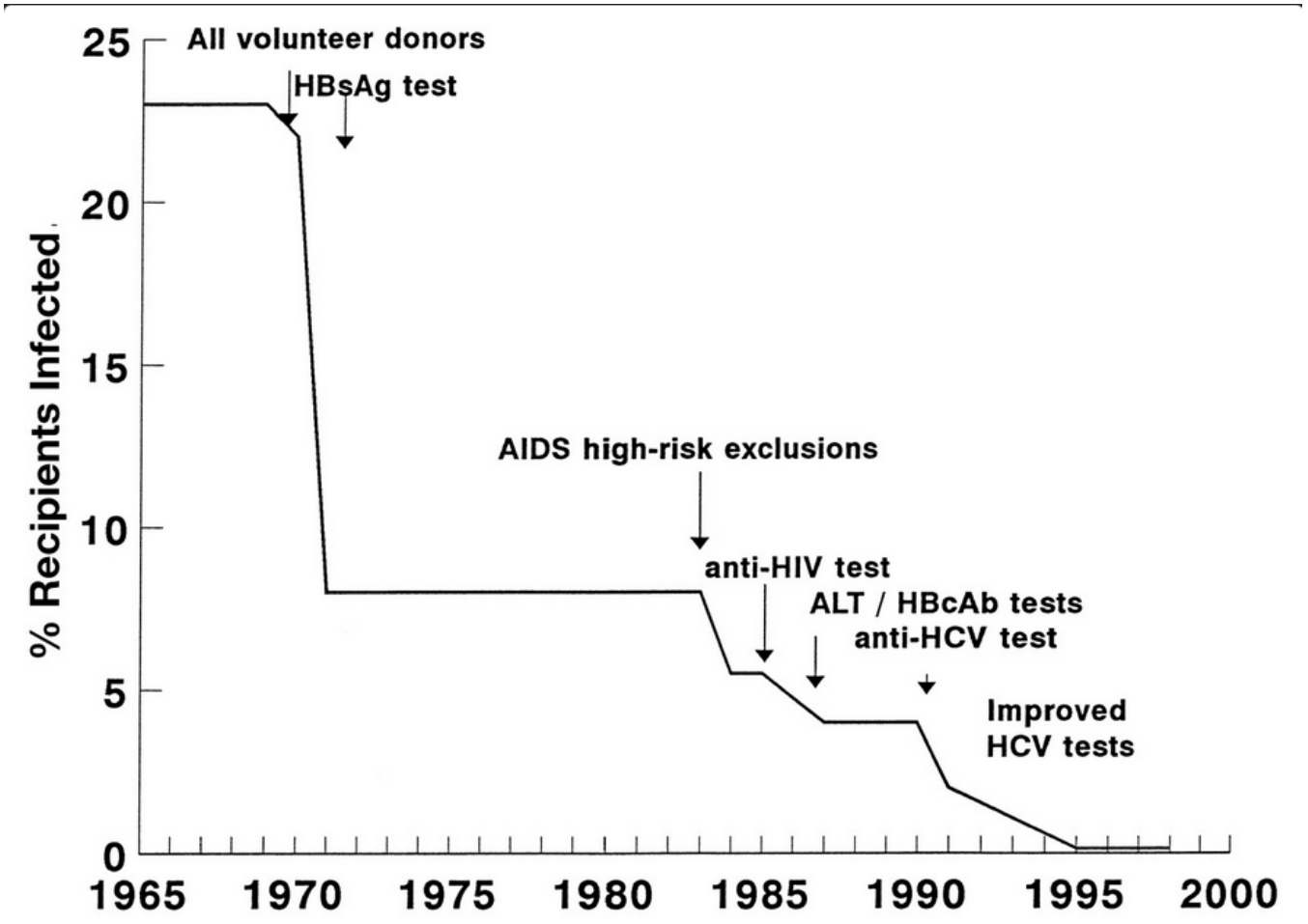
Participantes:

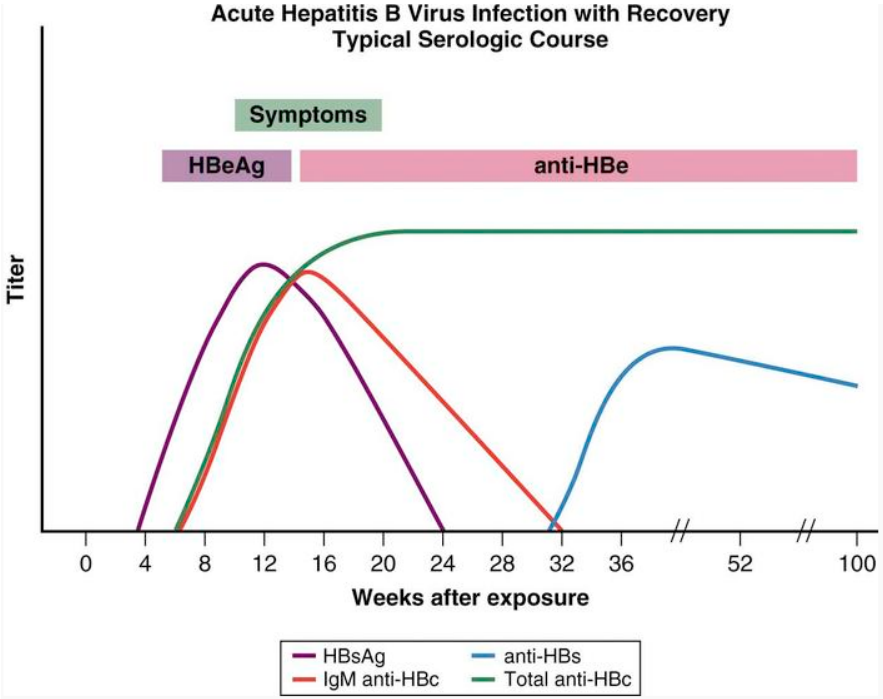
- Banc de Sang i Teixits. Barcelona
- Centro Regional de Transfusión Sanguínea de Córdoba
- Centro Regional de Transfusión Sanguínea de Málaga
- Centro Comunitario de Transfusión de Asturias
- Centro Vasco de Transfusión Sanguínea y Tejidos Humanos
- Fundacio Banc de Sang i Teixits de les Illes Balears
- Establecimiento de Tejidos Clínica San Francisco
- Banco de Sangre y Tejidos de Aragón
- Hospital Clínico San Carlos. Madrid
- Establecimiento de Tejidos CHUAC




HBsAg
Core
(HBcAg)
HBeAg
HBV DNA
Polymerase


Pacific
Ocean
Atlantic
Ocean
Indian
Ocean
Prevalence of
Hepatitis B
Surface Antigen
High ≥ 8%
Intermediate 2% – 7%
Low < 2%


All volunteer donors
HBsAg test
AIDS high-risk exclusions
anti-HIV test
ALT / HBcAb tests
anti-HCV test
Improved
HCV tests
% Recipients Infected
25
20
15
10
5
0
1965
1970
1975
1980
1985
1990
1995
2000


Acute Hepatitis B Virus Infection with Recovery
Typical Serologic Course
Symptoms
HBeAg
anti-HBe
Titer
0
4
8
12
16
20
24
28
32
36
52
100
Weeks after exposure
HBsAg
IgM anti-HBc
anti-HBs
Total anti-HBc

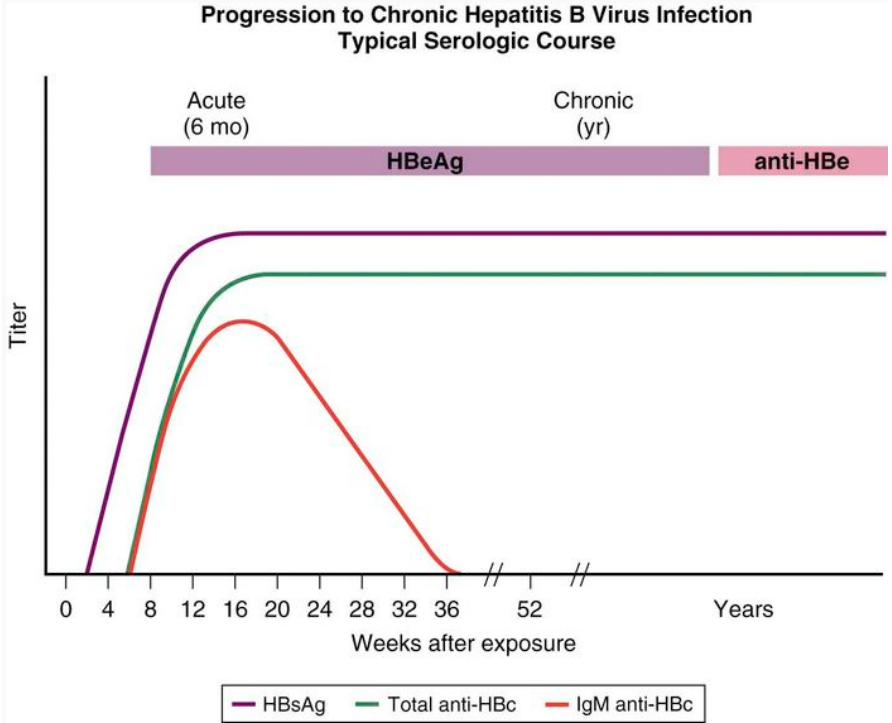

Progression to Chronic Hepatitis B Virus Infection
Typical Serologic Course
Acute
(6 mo)
Chronic
(yr)
HBeAg
anti-HBe
Titer
0
4
8
12
16
20
24
28
32
36
52
Years
Weeks after exposure
HBsAg
Total anti-HBc
IgM anti-HBc

Table 1: Interpretation of serologic tests for HBV adapted from (86)

HBsAg negative anti-HBc negative anti-HBs negative	No infection or immunity
HBsAg negative anti-HBc positive anti-HBs positive	Natural immunity
HBsAg negative anti-HBc negative anti-HBs positive	Vaccine immunity
HBsAg positive anti-HBc positive IgM anti-HBc positive anti-HBs negative	Acute infection
HBsAg positive anti-HBc positive IgM anti-HBc negative anti-HBs negative	Chronic infection
HBsAg negative anti-HBc positive anti-HBs negative	Four possible interpretations: 1. Resolved infection and immune (most common) 2. No infection or immunity (false-positive anti-HBc) 3. Occult chronic infection 4. Resolving acute infection

American Journal of Transplantation 2015; 15: 1162–1172
Wiley Periodicals Inc.

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doi: 10.1111/ajt.13187

Special Article

Solid Organ Transplantation From Hepatitis B Virus–Positive Donors: Consensus Guidelines for Recipient Management[†]

DIRECTIVA 2006/17/CE DE LA COMISIÓN

de 8 de febrero de 2006

por la que se aplica la Directiva 2004/23/CE del Parlamento Europeo y del Consejo en lo relativo a determinados requisitos técnicos para la donación, la obtención y la evaluación de células y tejidos humanos

ANEXO II

ANÁLISIS DE LABORATORIO A QUE DEBEN SOMETERSE LOS DONANTES DE CÉLULAS O TEJIDOS, CON EXCEPCIÓN DE LOS DONANTES DE CÉLULAS REPRODUCTORAS, MENCIONADOS EN EL ARTÍCULO 4, APARTADO 1

1. **Pruebas biológicas obligatorias para los donantes**

1.1. Todos los donantes tienen que someterse a las siguientes pruebas biológicas, como mínimo:

VIH-1,2	Anti VIH-1,2
Hepatitis B	HBsAg Anti HBc
Hepatitis C	Anti VHC-Ab
Sífilis	Véase el punto 1.4 (más adelante)

1.3. Si las pruebas anti HBc dan positivo y las pruebas HBsAg dan negativo, es preciso proseguir los exámenes de valoración del riesgo, para determinar la admisibilidad para uso clínico.

Donantes de Tejidos anticore positivo. ¿¿Problemas??

- En Portugal donante con **anti-core** positivo es una contraindicación.
- En USA ha sido contraindicación. En la actualidad se podrían realizar otros estudios.
- **Título de Antisuperficie**: No existe un acuerdo
  - Reino Unido: >100mlU/ml
  - Japón, Holanda: >200mlU/m
  - >10???

Cell Tissue Banking (2007) 8:303–305
DOI 10.1007/s10561-007-9039-y

BRIEF COMMUNICATION

Evaluation of tissue discards after implementation of anti-HBc test in a tissue bank in Spain

Rafael Villalba · Gema Fornés · Marcela Eisman · Jose Luis Gómez Villagrán

Table 1 Hepatitis B markers in 911 tissue donors

Variable	*n*	(%)
HBs Ag +	8	(0,9)
Anti-HBc +	160	(17,6)
Anti-HBc only[a]	38	(4,2)

[a] Anti-HBc positive plus Anti-HBs <10 mUI/ml

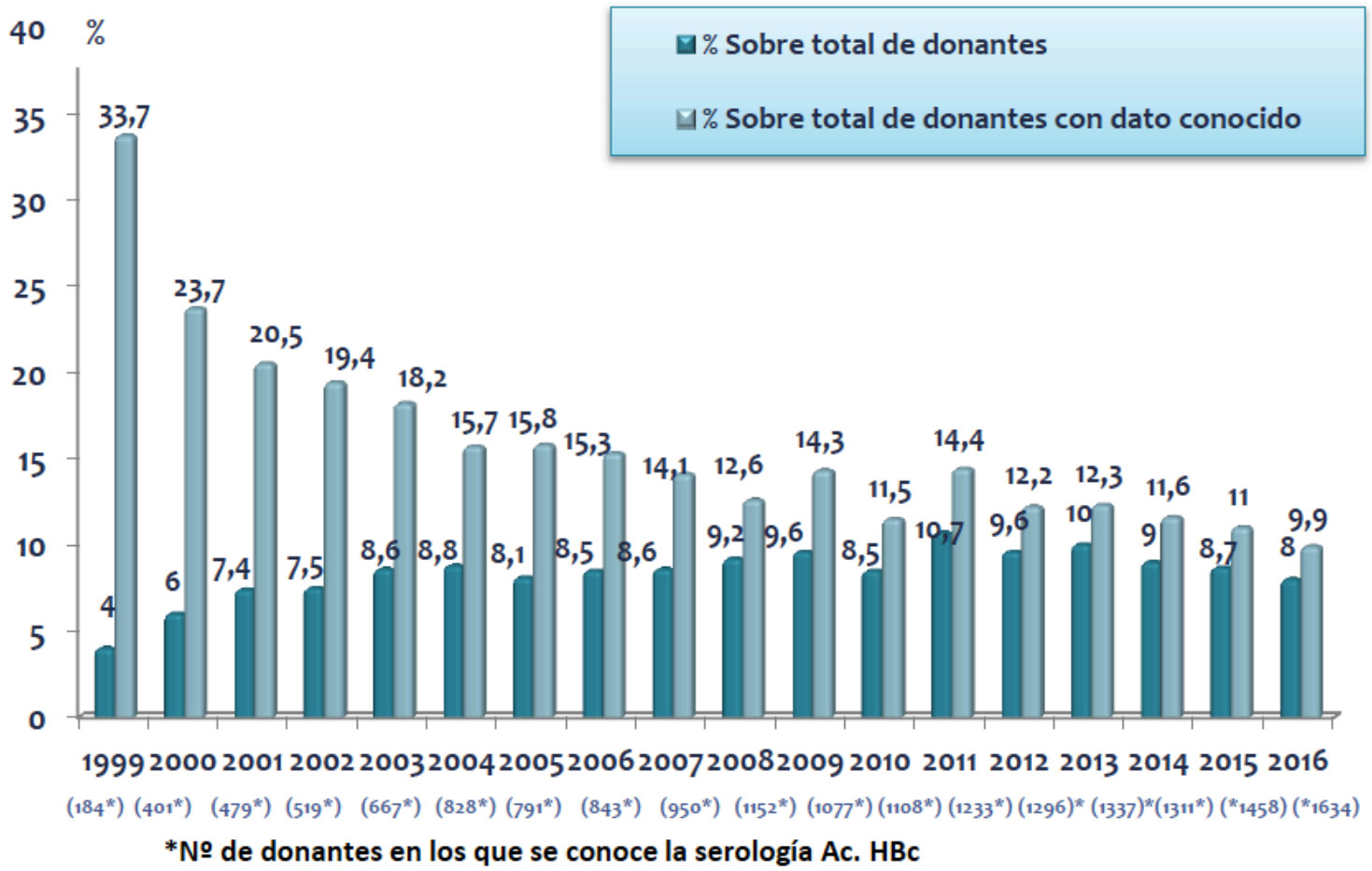


Figura 41: Prevalencia de positividad para Anti-HBc en donantes de órganos. España 1999-2016. Se proporciona el dato sobre el total de donantes y sobre el nº de donantes de los que se conoce la serología Ac HBc.

ELSEVIER

Risk of Transmission of Hepatitis B Virus From Anti-HBc Positive Cadaveric Organ Donors: A Collaborative Study

T.M. De Feo, F. Poli, F. Mozzi, M.P. Moretti, M. Scalamogna, and Collaborative Kidney, Liver and Heart North Italy Transplant program Study Groups

Table 1. Incidence of Seroconversion to HBsAg+

	Kidney		Liver		Heart	
Recipient HBV Profile	Pretransplant	Seroconversion	Pretransplant	Seroconversion	Pretransplant	Seroconversion
HBsAg +	12	—	12	—	2	—
R +	177	0	35	0	5	0
R−	62	0	14	6 (43%)	18	0
Total	251	0	61	6	25	0

R+: recovered or immunized.
R−: naïve (HBs Ag-/anti-HBs-/anti-HBc-).

Year	Country
1997	Germany
1999	Austria, Japan
2004	Singapore, Spain
2005	Poland, France (OT + army), South Africa
2006	Greece, Italy, Portugal, Thailand
2007	Hong Kong, Kuwait, Malaysia, New Zealand, Slovenia, Switzerland
2008	Finland, Israel, Latvia, Netherlands, Taiwan
2009	United States, Denmark, Ireland, United Kingdom (England and Wales)
2010	Australia, United Kingdom (Scotland), Canada
2012	South Korea

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 19, 2004 VOL. 351 NO. 8

Probability of Viremia with HBV, HCV, HIV, and HTLV among Tissue Donors in the United States

Shimian Zou, Ph.D., Roger Y. Dodd, Ph.D., Susan L. Stramer, Ph.D., and D. Michael Strong, Ph.D., for the Tissue Safety Study Group

PROBABILITY OF VIREMIA AMONG U.S. TISSUE DONORS

Table 4. Estimated Probability of Viremia Undetected by Testing Methods at the Time of Tissue Donation, According to the Blood-Donor Approach and the General-Population Approach.*

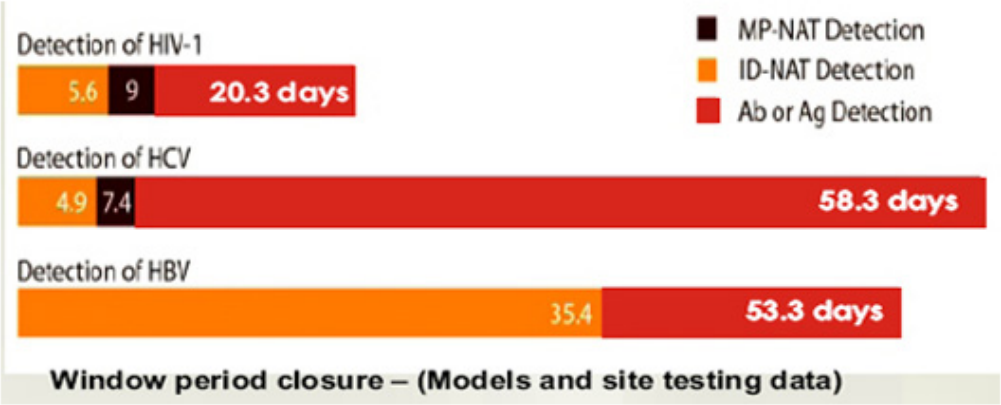
Agent	Window Period†	Estimated Incidence		Estimated Probability		Nucleic Acid–Amplification Testing	
		Blood-Donor Approach	General-Population Approach	Blood-Donor Approach	General-Population Approach	Window Period‡	Projected Probability§
	days	*no./100,000 person-yr*		*no./100,000 tissue donors (95% CI)*		*days*	*no./100,000 tissue donors*
HIV antibody	22	30.118	7.099	1.815 (0.577–4.451)	0.428	7	0.578
HBsAg	59	18.325	15.100	2.962 (1.466–5.254)	2.441	20	1.004
HCV antibody	70	12.380	4.910	2.374 (1.367–6.002)	0.942	7	0.237
HTLV antibody	51	5.586	—	0.780 (0.344–2.432)	—	—	—

* The blood-donor and general-population approaches are explained in the Methods section. No data on HTLV were available for use with the general-population approach. CI denotes confidence interval.

† Data on the window periods are from Dodd et al.[11]

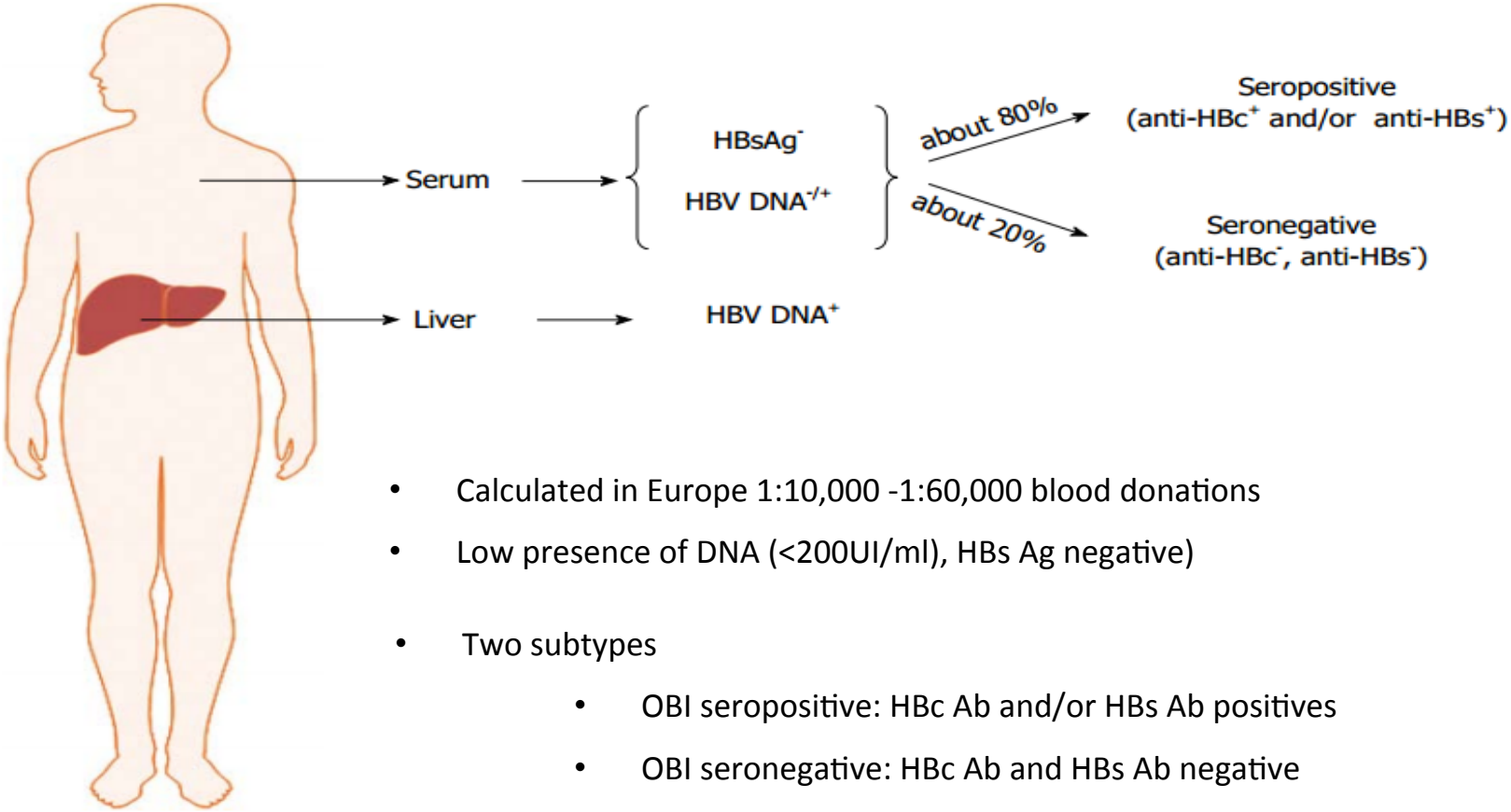
‡ Data on the window periods are from Jackson et al.[19]

§ Values are the projected probability of collecting tissues from donors during the viremic window period for HIV, HCV, and HBV infections after the implementation of nucleic acid–amplification testing of individual specimens.



Busch et al. Transfusion. 2005;45(2):254-264., Kleinman and Busch,
J Clin Virol, 2006;36:S23-S29. Data on file at Chiron, Novartis Vaccines and Diagnostics, Inc.

SEROLOGICAL PATTERN OF OCCULT HEPATITIS B INFECTION



- Calculated in Europe 1:10,000 -1:60,000 blood donations
- Low presence of DNA (<200UI/ml), HBs Ag negative)
- Two subtypes
  - OBI seropositive: HBc Ab and/or HBs Ab positives
  - OBI seronegative: HBc Ab and HBs Ab negative

Figure 1 Schematic representation of hepatitis B virus profiles in occult hepatitis B virus infection. HBV: Hepatitis B virus.

Vox Sanguinis (2008) **94**, 153–166

INTERNATIONAL FORUM

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Journal compilation © 2008 Blackwell Publishing Ltd.

Vox Sanguinis

Occult hepatitis B infection in blood donors

H. W. Reesink, C. P. Engelfriet, G. Henn, W. R. Mayr, G. Delage, F. Bernier, T. Krusius, A. Assal, P. Gallian, C. Corbi, P. Morel, B. David, P. De Micco, H. Murokawa, H. Yugi, S. Hino, K. Tadokoro, Ø. Flesland, E. Brojer, M. Łętowska, G. Olim, F. Nascimento, H. Gonçalves, L. Castro, M. Morais, S. L. Stezinar, M. Alvarez, S. Sauleda, R. González, C. Niederhauser, M. Stolz, J.-P. Allain, S. Owusu-Ofori, R. Eglin, S. Stramer, M. Busch, D. M. Strong, J. Epstein, R. Biswas

Table 1 Occult hepatitis B virus (HBV) infections (OBI) in random donors screened by HBV DNA NAT

Country	Year of introduction	HBV DNA+ *n*/total	Prevalence of OBI	Technique(s) used	Pool size	Remarks
Poland	2005	31/1 962 036	1 : 63 000	Roche Chiron	1 : 24 (2006) 1 : 6 (2007)	5/31 OBI were WP infections (1 : 490 000)
Portugal	2006	3/174 074	1 : 50 000	Roche Chiron	1 : 6 ID	
Spain	2004–2006	39/1 641 891	1 : 42 000	Roche Chiron in house	ID 1 : 6 1 : 8	15/24 centres implemented HBV NAT
Slovenia	2007	4/30 000	1 : 7500	Chiron	ID	
Japan	1999	381/40 591 962	1 : 107 000	Roche multiplex	1 : 500 (1999) 1 : 50 (2000) 1 : 20 (2004)	40% WP and 60% tail-end OBI
Ghana	2005/06	3/18 400	1 : 60 000	in house	?	Study only
French Antilles and La Réunion	2005	0/74 959	?	Chiron	ID	

ID, individual donor; WP, window period.

Infectivity of blood products from donors with occult hepatitis B virus infection

Jean-Pierre Allain, Ivanka Mihaljevic, Maria Isabel Gonzalez-Fraile, Knut Gubbe, Lene Holm-Harritshøj, Jose Maria Garcia, Ewa Brojer, Christian Erikstrup, Mona Saniewski, Lorenz Wernish, Lydia Bianco, Henrik Ullum, Daniel Candotti, Nico Lelie, Wolfram H. Gerlich, and Michael Chudy

- Riesgo de transmisión: **28%** (**63,8%** en receptores no vacunados)
- Riesgo de transmisión con productos *antisuperficie* positivos: **15,4%**
- Dosis mínima infecciosa 50%: **1049** copias (**117** – **3441**)
- Riesgo de transmisión con productos antisuperfice negativos (Depende del volumen de plasma infundido):
    - -A) **85 – 100%** con 200 ml de Plasma fresco congelado
    - -B) **51%** con 50 ml de Concentrado de Plaquetas
    - - C) **24%** con 20 ml de Concentrado de Hematíes

Guide to the preparation, use and quality assurance of BLOOD COMPONENTS

European Committee (Partial Agreement) on Blood Transfusion (CD-P-TS)

EDQM
19th Edition
2017

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COUNCIL OF EUROPE

Anti-HBc screening

Donors or donations may be tested by an approved test that will detect antibodies to hepatitis B core antigen (anti-HBc). The approach to deferral or re-entry of an anti-HBc positive donor should be established in an algorithm.

Re-entry into the donor base of an anti-HBc positive donor and the subsequent release of his/her donations should only be considered when the donor has been shown to have anti-HBs with a titre of at least 100 IU/L and each subsequent donation should test negative for both HBsAg and HBV DNA using approved assays.

Cell Tissue Bank
DOI 10.1007/s10561-015-9539-0

BRIEF COMMUNICATION

Nucleic acid-amplification testing for hepatitis B in cornea donors

Maria Gema Fornés · Maria Angustias Jiménez · Marcela Eisman · Jose Luis Gómez Villagrán · Rafael Villalba

Table 1 Results of tissue donors

Donors (sex/age)	HBsAg	HBc Ab[a]	HBs Ab (mIU/mL)[b]	NAT	DHBV[c]	Viral load PCR (UI/ml)
1:F/62	NEG	POS	>1000	POS	POS	137
2:M/56	NEG	POS	>1000	POS	NEG	<20
3:M/56	NEG	POS	48.04	POS	POS	170

[a] Hepatitis B core antibody (HBc Ab)

[b] Hepatitis B surface antibody (HBs Ab)

[c] Discriminatory assay for HBV

Cell Tissue Bank (2017) 18:335–341
DOI 10.1007/s10561-017-9644-3

FULL LENGTH PAPER

Detection of hepatitis B virus in bone allografts from donors with occult hepatitis B infection

Vicente Mirabet · Manuel Álvarez · Mar Luis-Hidalgo · Juan Galán · Nieves Puig · Luis Larrea · Cristina Arbona

Table 1 continued

Donor									Tissue				
Number	Sex	Age	Serology				NAT		Type	Storage (days at −80 °C)	Concentration (g/mL)	NAT	
			HBsAg S/CO	Anti-HBc S/CO	Anti-HBe	Anti-HBs IU/L	Screening	Discrim. HBV				Screening	Discrimina HBV
3	Female	86	Neg 0.07	Pos <0.1	Pos	0	Pos	Pos	Femoral head	556	0.43	Pos 1/4 S/CO 2.31	Neg 4/4
9	Male	61	Neg 0.09	Pos <0.1	Not done	0	Neg/Pos	Neg	Femoral Condyle Med-Right	42	0.57	Neg 2/2	Pos 1/4 S/CO 16.14
									Femoral Condyle Lat-Right	42	1.40	Neg 1/1	Pos 1/1 S/CO 12.03
											1.06	Pos 1/2 S/CO 10.83	Neg 1/1
									Femoral Condyle Med-Left	42	0.83	Pos 1/2 S/CO 12.29	Not done
											0.71	Pos 2/2 S/CO 11.75	Neg 2/2
									Femoral Condyle Lat-Right	42	0.50	Pos 5/7 S/CO 13.8	Neg 1/1

Propuesta de estudio

- Evaluar los marcadores de hepatitis B en donantes de tejidos a nivel nacional.
- Se excluyó tejido reproductor, donantes de células madre hematopoyéticas y pacientes craneoplastias autólogas.
- Establecer recomendaciones para Coordinadores de Trasplantes y Bancos de Tejidos.

Casos:

- Banc de Sang i Teixits. Barcelona 389
- Establecimiento de Tejidos CHUAC 146
- Centro Vasco de Transfusión Sanguínea y Tejidos Humanos 111
- Centro Regional de Transfusión Sanguínea de Córdoba

  100
- Fundacio Banc de Sang i Teixits de les Illes Balears 61
- Establecimiento de Tejidos Clínica San Francisco 47
- Centro Comunitario de Transfusión de Asturias 36
- Banco de Sangre y Tejidos de Aragón

  34
- Centro Regional de Transfusión Sanguínea de Málaga 25
- Establecimiento de Tejidos. Hospital Clinico Madrid 19

Características demográficas

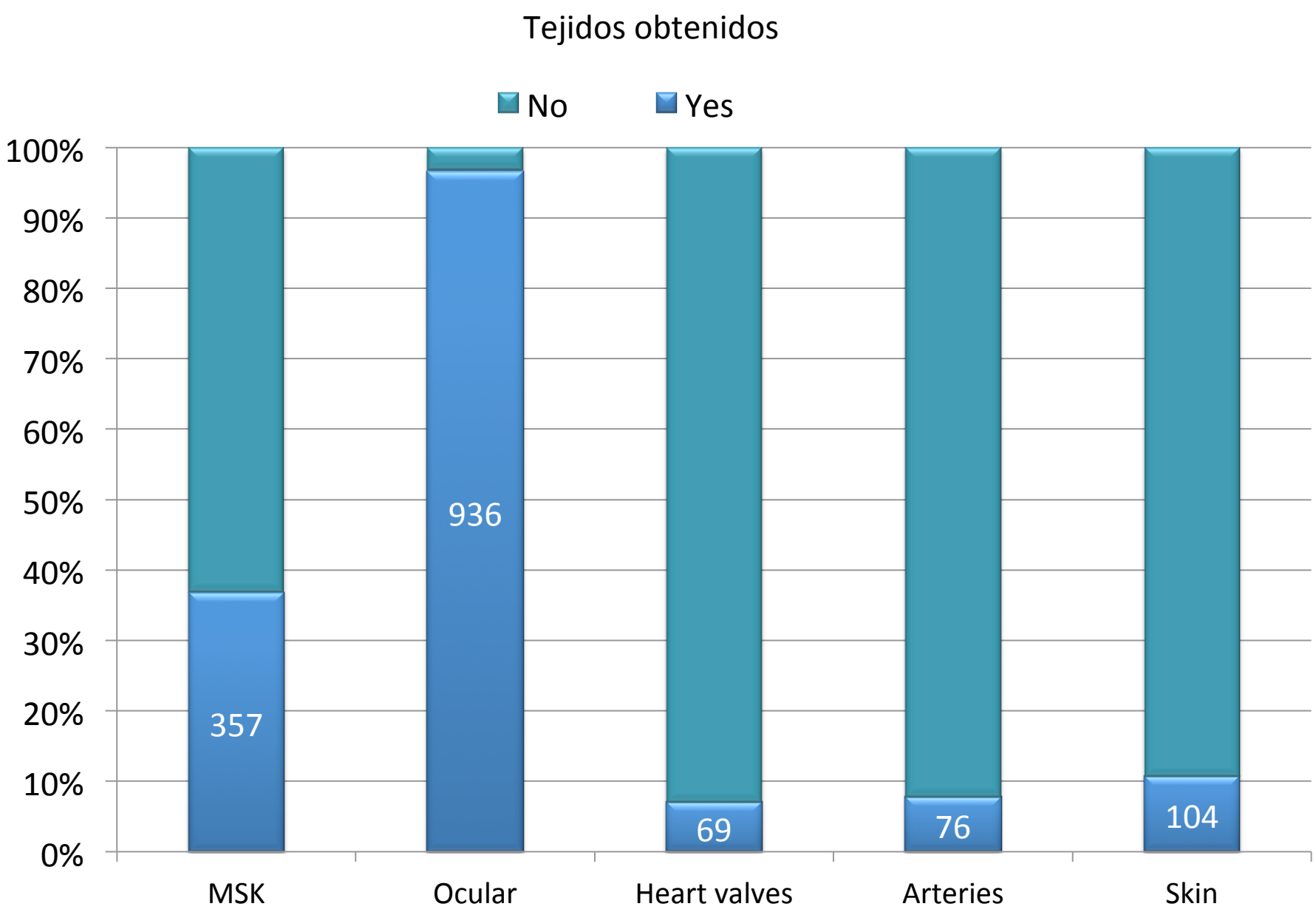
Hombres	625 (64.6%)
Mujeres	343 (35.4%)
Edad	63 ±15 (1-89) años
Donante de órganos y tejidos	409 (42.3%)
Donante solo tejidos	559 (57.7%)
Antecedente tumoral	197 (20.4%)
Sin antecedente tumoral	771 (79.6 %)

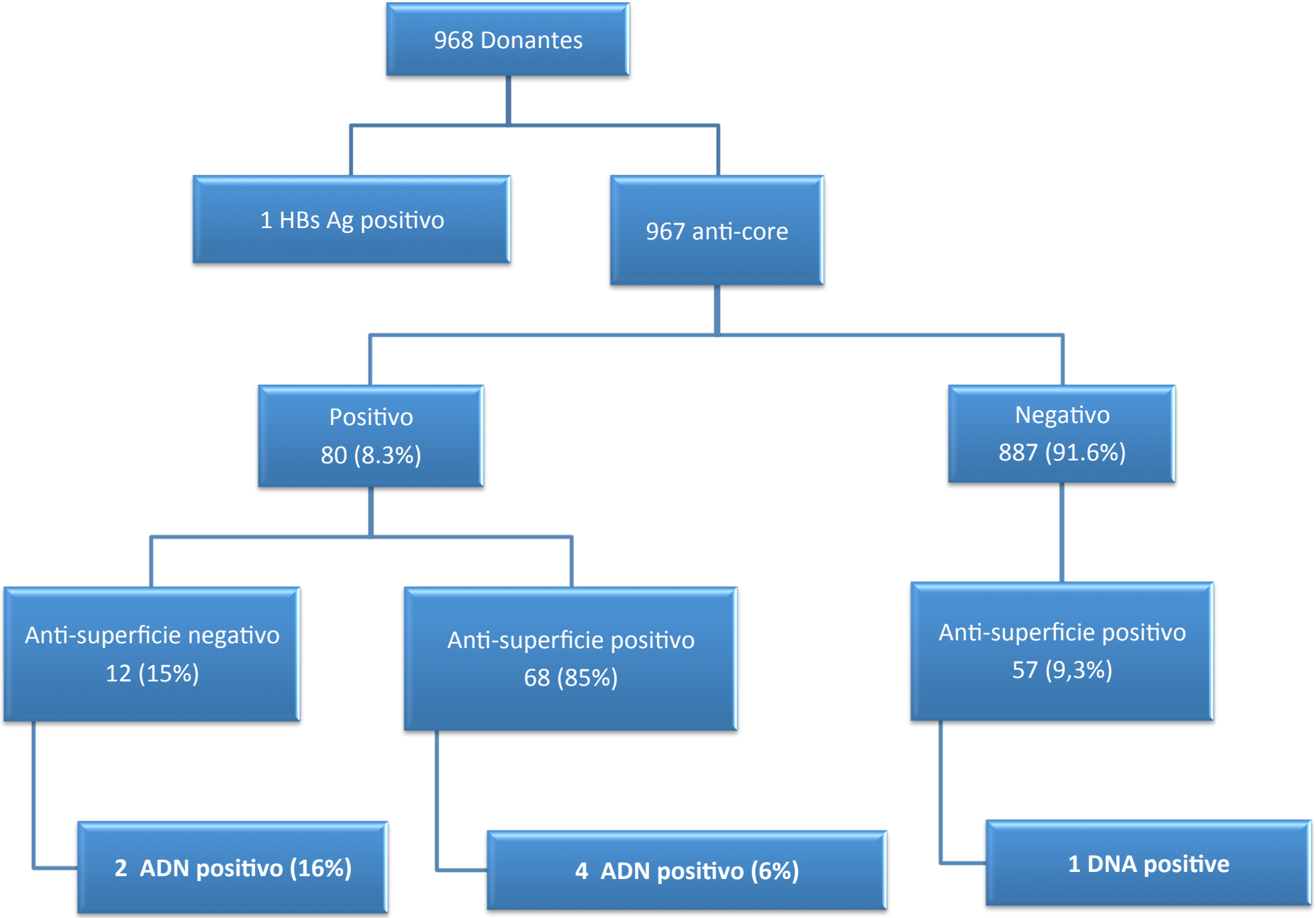
Causa de muerte

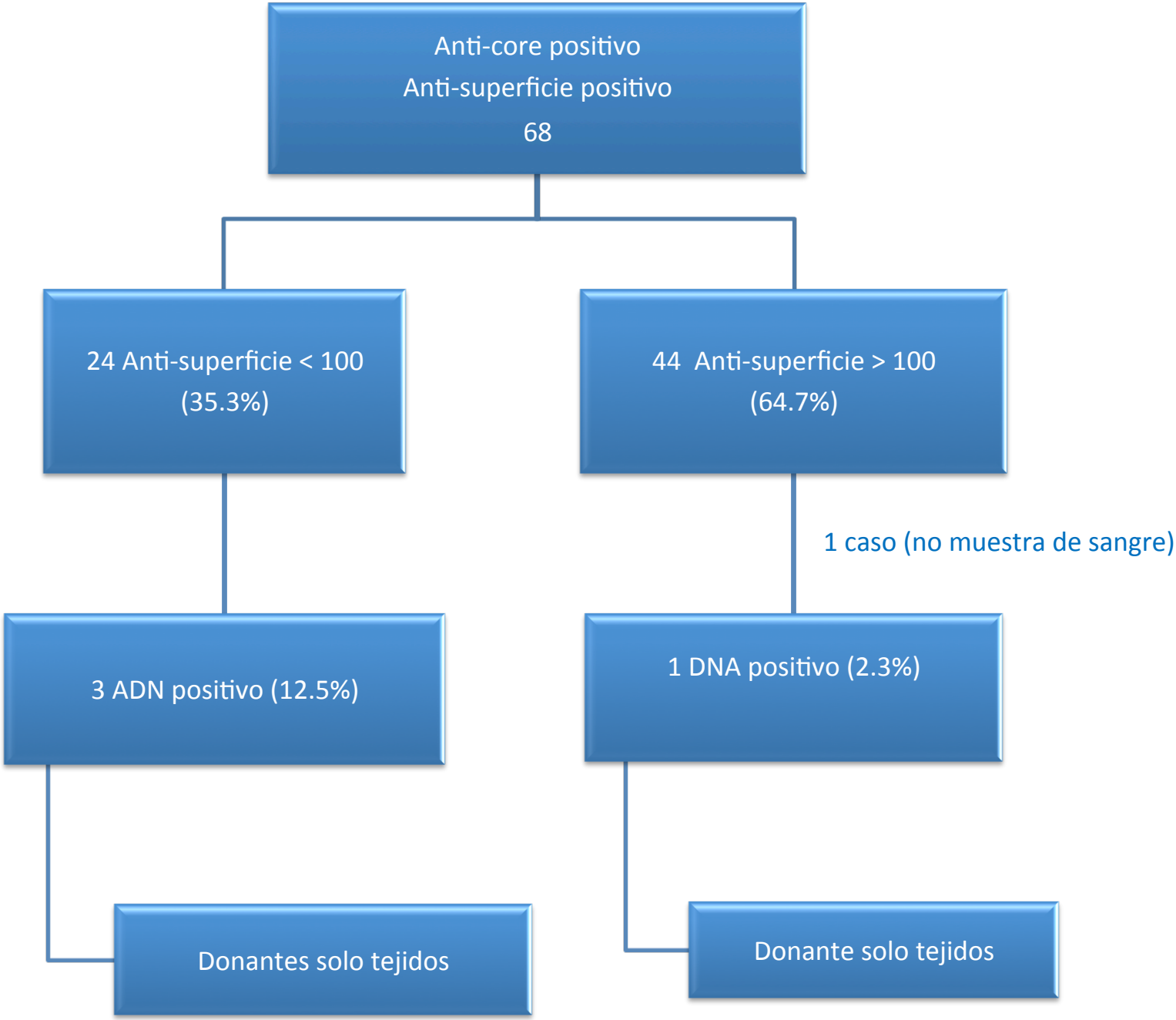
Brain hemorrhage	346 (35.7%)
Tumor	177 (18.3%)
Heart problems	138 (14.3%)
Brain Anoxia	113 (11.7%)
Brain Trauma	77 (8%)
Lung problems	74 (7.6%)
Hypovolemic	14 (1.4%)
Hepatic insufficiency	10 (1%)
Others	10 (1%)
Septic shock	6 (1%)
No diagnosis	3 (0,5%)

Tipo de tumor

Lung	61 (31%)
Gastrointestinal	61 (31%)
Urological	25 (12.7%)
Breast cancer	22 (11.2%)
Gynecological	10 (5.1%)
Otorhinolaryngology	8 (4.1%)
Central nervous system	2 (1%)
Others	8 (4%)


Tejidos obtenidos
No
Yes
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
357
936
69
76
104
MSK
Ocular
Heart valves
Arteries
Skin


968 Donantes
1 HBs Ag positivo
967 anti-core
Positivo
80 (8.3%)
Negativo
887 (91.6%)
Anti-superficie negativo
12 (15%)
Anti-superficie positivo
68 (85%)
Anti-superficie positivo
57 (9,3%)
2 ADN positivo (16%)
4 ADN positivo (6%)
1 DNA positive


Anti-core positivo
Anti-superficie positivo
68
24 Anti-superficie < 100
(35.3%)
44 Anti-superficie > 100
(64.7%)
1 caso (no muestra de sangre)
3 ADN positivo (12.5%)
1 DNA positivo (2.3%)
Donantes solo tejidos
Donante solo tejidos

	Anti-core positivo	Anti-core negativo	*p*
Edad	**68±15 años**	**62.6 ± 15 años**	**0.001**
Hombres	8 %	92 %	0.677
Mujeres	8.8 %	91.2 %	
Donante de órganos y tejidos	6.6 %	93.4 %	0.106
Donante tejidos	9.5 %	90.5 %	
Tumoral	8.6 %	91.4 %	0.839
No tumoral	8.2 %	91.8 %	
Muestra *Premortem*	8.7 %	91.3 %	0.819
Muestra *Postmortem*	8.3 %	91.7 %	
Muestra (tiempo isquemia caliente)	233.4 minutes	250.5 minutes	0.703
Muestra (tiempo isquemia fría)	506.4 minutes	382.6 minutes	0.289
Área Mediterránea	8.4 %	91.6 %	0.538
Área norte	8.2 %	91.8 %	
Área sur	10.5 %	89.5 %	
Área central	4.8 %	95.2 %	

Conlusiones

- Incidencia de anti-core positivo en donantes de tejidos en España: **8.3 %**
- No existen diferencias respecto al tipo de donante (órganos / tejidos, tumoral no tumoral)
- Donantes mayores
- Donantes ***core aislado*** : 2 casos ADN positivo (**16%**)
- Donantes con ***antisuperficie positivo***: 4 casos ADN positivo (**6%**)
  - Título < 100 UI: 3 casos ADN positivo (**12,5%**)
  - Títulos ≥100 UI: 1 caso ADN positivo (**2,3%**)

- **ADN positivo** (HBsAg negativo): 7 casos, total **(0.7%)**

- Cuando realizar determinación ADN
  - Siempre?
  - Anti-core negativo y anti-superficie negativo: resulta necesario?
  - Problemas con el donante de córneas

- Título de antisuperficie
  - Solo ≥ 100 UI serían aceptables??
  - Menos de 100 UI sería rechazo? (**3,7%** de donantes)
  - Entre 10-100?
  - No importa el título si se realiza ADN (**0,7%** donantes)? Si es negativo es aceptable?

Muchas grácias

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