NOTIFY LIBRARY

The NOTIFY project - a general overview

Update October 2024

Centro Nazionale Trapianti
Italian National Transplant Centre

WHO Collaborating Centre on Vigilance and Surveillance for Human Cells, Tissues and Organs

WORLD HEALTH ASSEMBLY RESOLUTION WHO 63.22

Resolution 63.22 of the World Health Assembly was adopted in 2010 and gave WHO a mandate to facilitate Member State access to appropriate informations on donation, processing and transplantation of tissues, cells and organs, including data about serious adverse events and reactions.

NOTIFY PROJECT

World Health Organization

Centro Nazionale Trapianti

SohoVaS Public Health

Sharing vigilance experience and knowledge globally
- the NOTIFY Project (WHO)

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NOTIFY PROJECT: AIMS

To provide professionals with relevant information helpful for determining the suitability of a potential donor.

To draft common guidelines supporting the implementation of effective vigilance and surveillance

To provide practical support to countries that are developing vigilance systems for Medical Products of Human Origin (MPHO)

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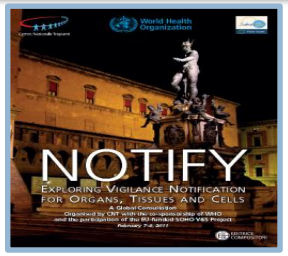
NOTIFY – Timeline

2010 — The NOTIFY Google Site

2011 — BOLOGNA: The Bologna Meeting



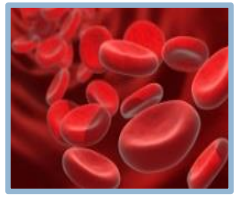
2012 — GENEVA: BIG V&S - First Global Consultation on V&S

ROME: Second Global Consultation

2013 — BRASILIA: Third Global Consultation

Notify Booklet

2014 — BARCELONA: Haemovigilance



2015 — BARCELONA: Technical Meeting

Bologna: Strategic Meeting

2016 — ROME: Second Technical Meeting

Joint global initiative (WHO, CNT, SOHO V&S) to raise the profile of V&S of SOHO. Adoption of Resolution 63.22 by the World Health Assembly

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NOTIFY – HISTORY

2018

BRUSSELS

Global Vigilance Networking NOTIFY and VISTART joint meeting

2019

Cairo

How to Build a Vigilance System

2020

Stockholm

Virtual Conference

Joint ECDC and Notify Project Meeting

2021

Journal Publications

2022

Rome

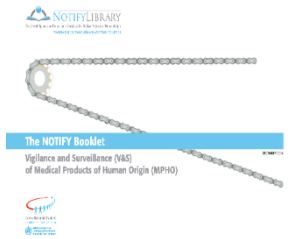
Technical Meeting

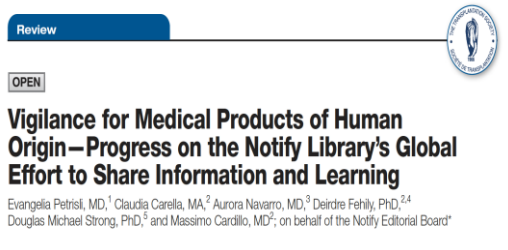
2024

Washington DC

Technical meeting

Update Booklet II edition

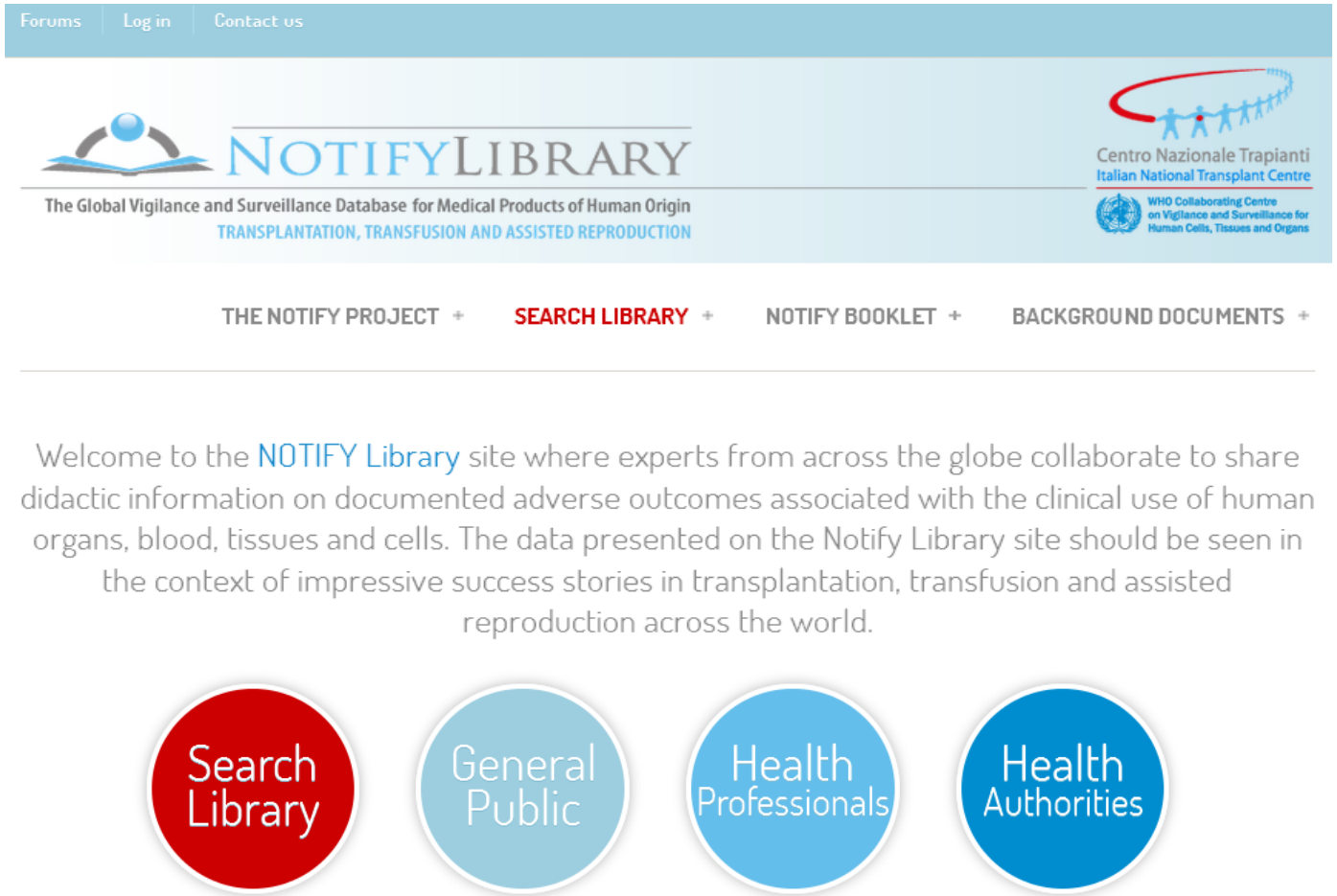




NOTIFYLIBRARY

http://www.notifylibrary.org

Communication hub for institutions and organisations worldwide collaborating in the facilitation of access to V&S information



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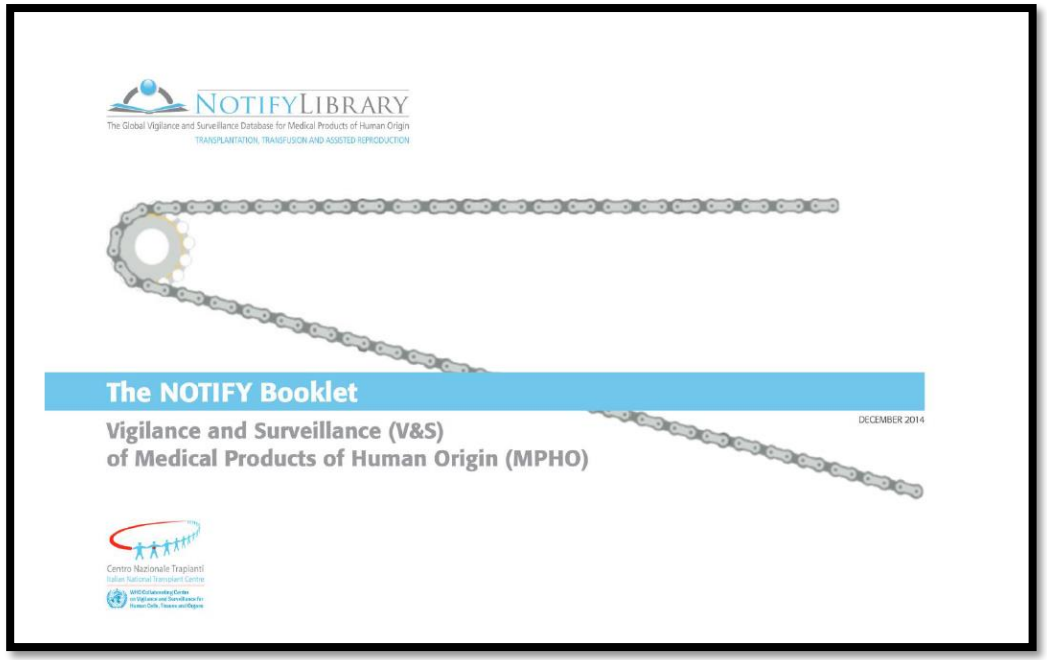
NOTIFY BOOKLET

NOTIFY Booklet

I edition



II edition - 2018

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BACKGROUND DOCUMENTS

VIGILANCE GUIDANCE DOCUMENTS

- Council of Europe – European directorate for the quality of Medicine and HealthCare (EDQM), European Centre for Disease Prevention and Control (ECDC), International Haemovigilance Network (IHN), International Society of Blood Transfusion (ISBT), ecc

VIGILANCE AND SURVEILLANCE REPORTS

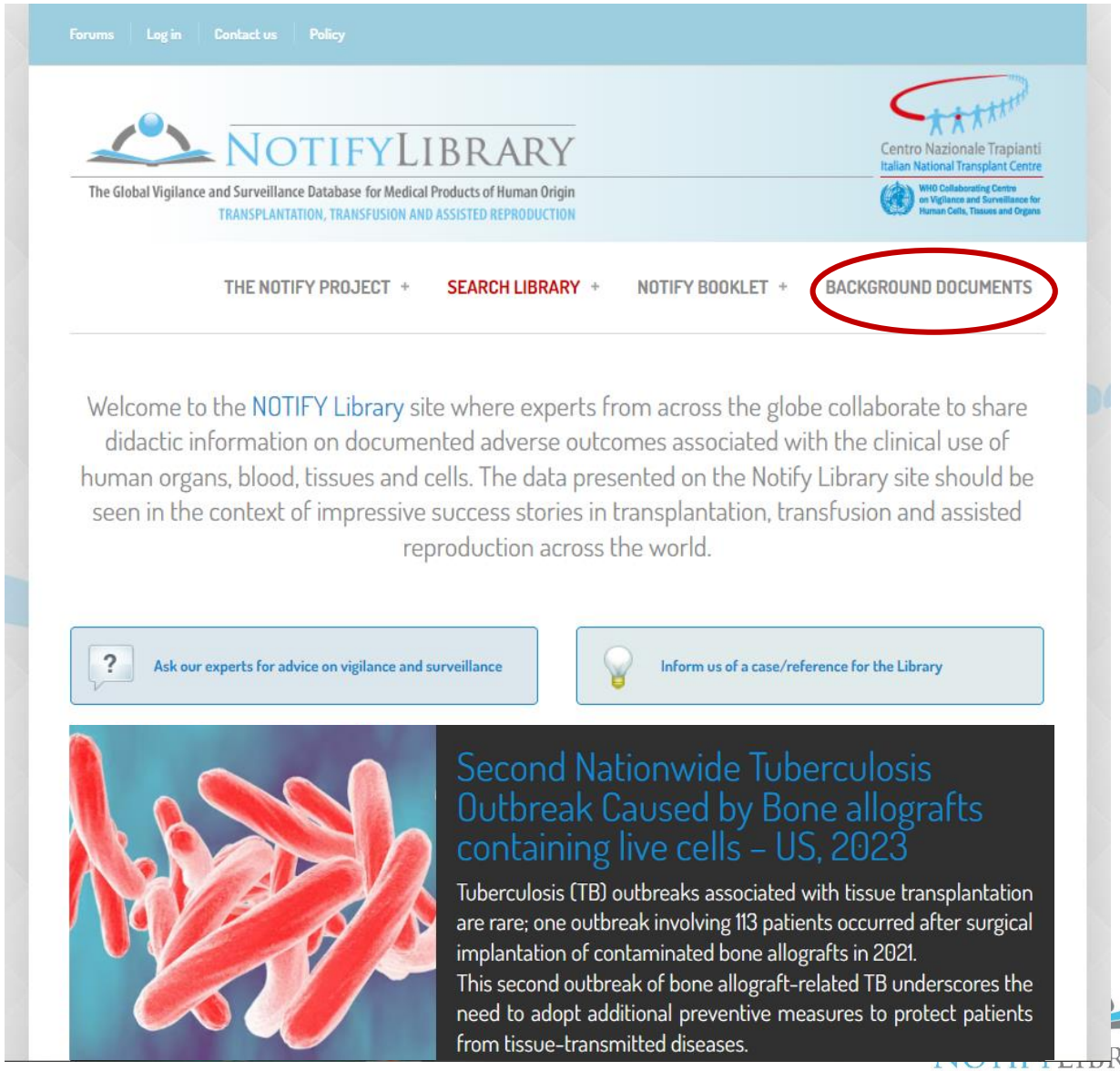
- European Union Annual Vigilance Reports, American Association of Blood Banks (AABB), Food and Drug Administration (FDA), Human Fertilisation and Embryology Authority (HFEA), Transfusion and Transplantation Reactions in Patients (TRIP), World Marrow Donors Association (WMDA), ecc

WORLD HEALTH ORGANISATION (WHO) AND WORLD HEALTH ASSEMBLY (WHA)

- WHO Guiding Principles on Transplantation, WHO Aide Memoire for National Health Authorities on Safety and Quality of T&C, WHO Consultation Report – Tissues and Cells., WHA Resolution 63.22.2010

RECOMMENDATION FOR EPIDEMIC DISEASE OCCURRENCE

- Zika Virus (archived)
- SARS-CoV-2
- Monkeypox Virus (MPXV)



The NOTIFY Library

- publically accessible online database of didactic cases of severe adverse reactions and events
- from procurement and processing to clinical application of blood, organs, tissues and cells used in transfusion, transplantation and assisted reproduction
- collected and analyzed by **5 dedicated editorial groups** of international experts, regulators and clinicians and linked to their source reference:
  - literature review (published articles in scientific journals and/or books)
  - case reports from regulatory or professional vigilance programs (grey literature)

REFERENCE SOURCES

Literature review

Query based automated bibliographic search (Ovid, Google Scholar)

Individual notifications (Editorial group members, other health professionals)

Grey literature

Reports from partner organizations (Competent Authorities, professional associations)

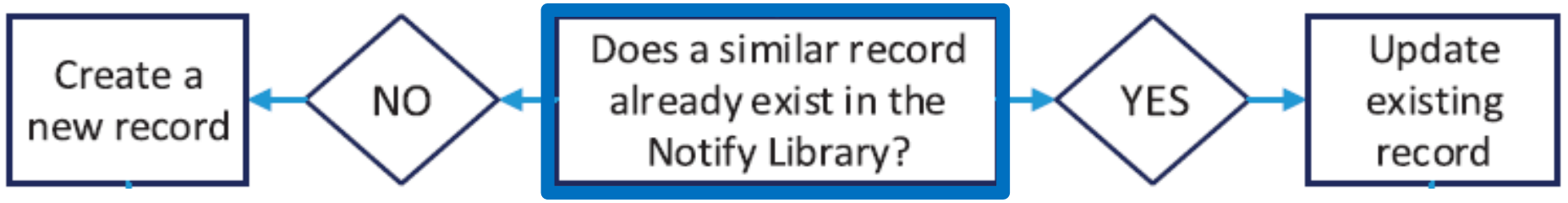
EIOS EPIDEMIC INTELLIGENCE FROM OPEN SOURCES

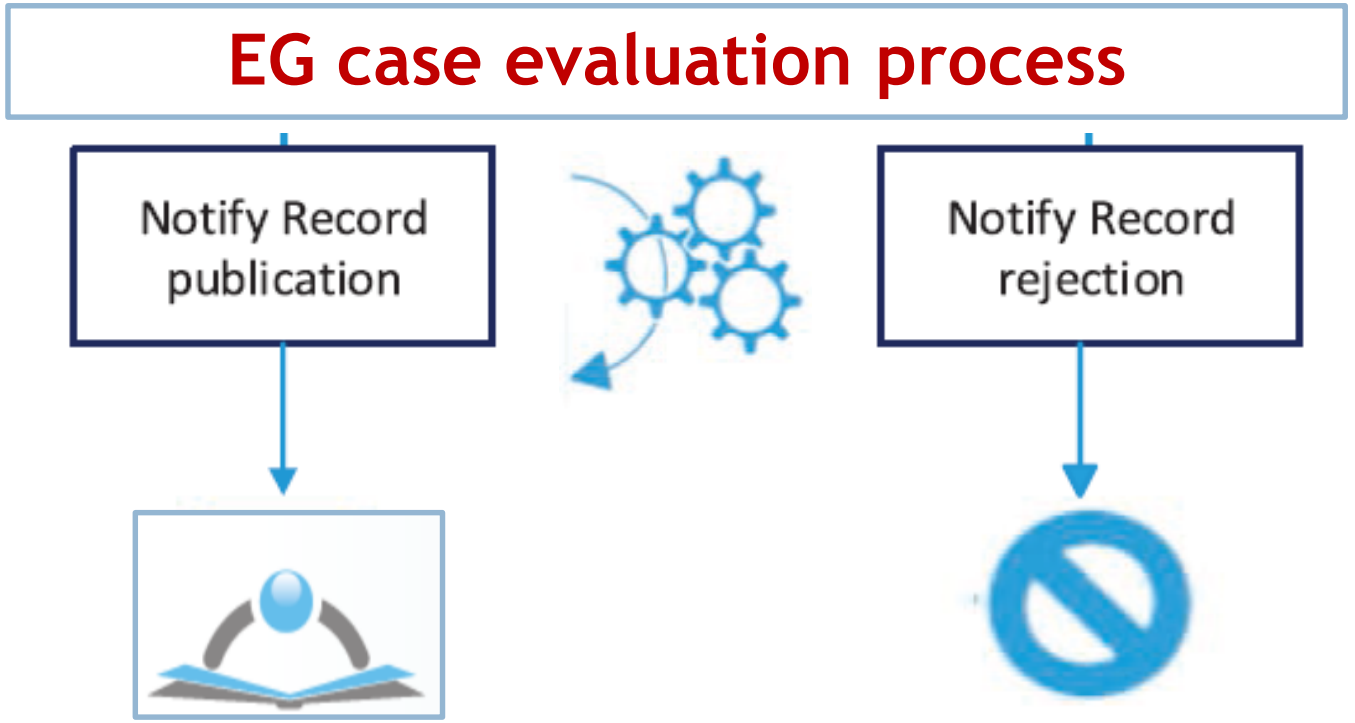
MPHO Safety Network

Inclusion criteria

1. It describes an adverse occurrence that has caused **harm** to a donor or a recipient of an MPHO or to a fetus or embryo created through gamete or embryo donation or an adverse occurrence that has presented a **risk of harm**;
2. It is **reliably documented** in the scientific, clinical, or legal literature or in a formal professional or regulatory vigilance program;
3. It has **instructive value**.

WORKING METHODOLOGY





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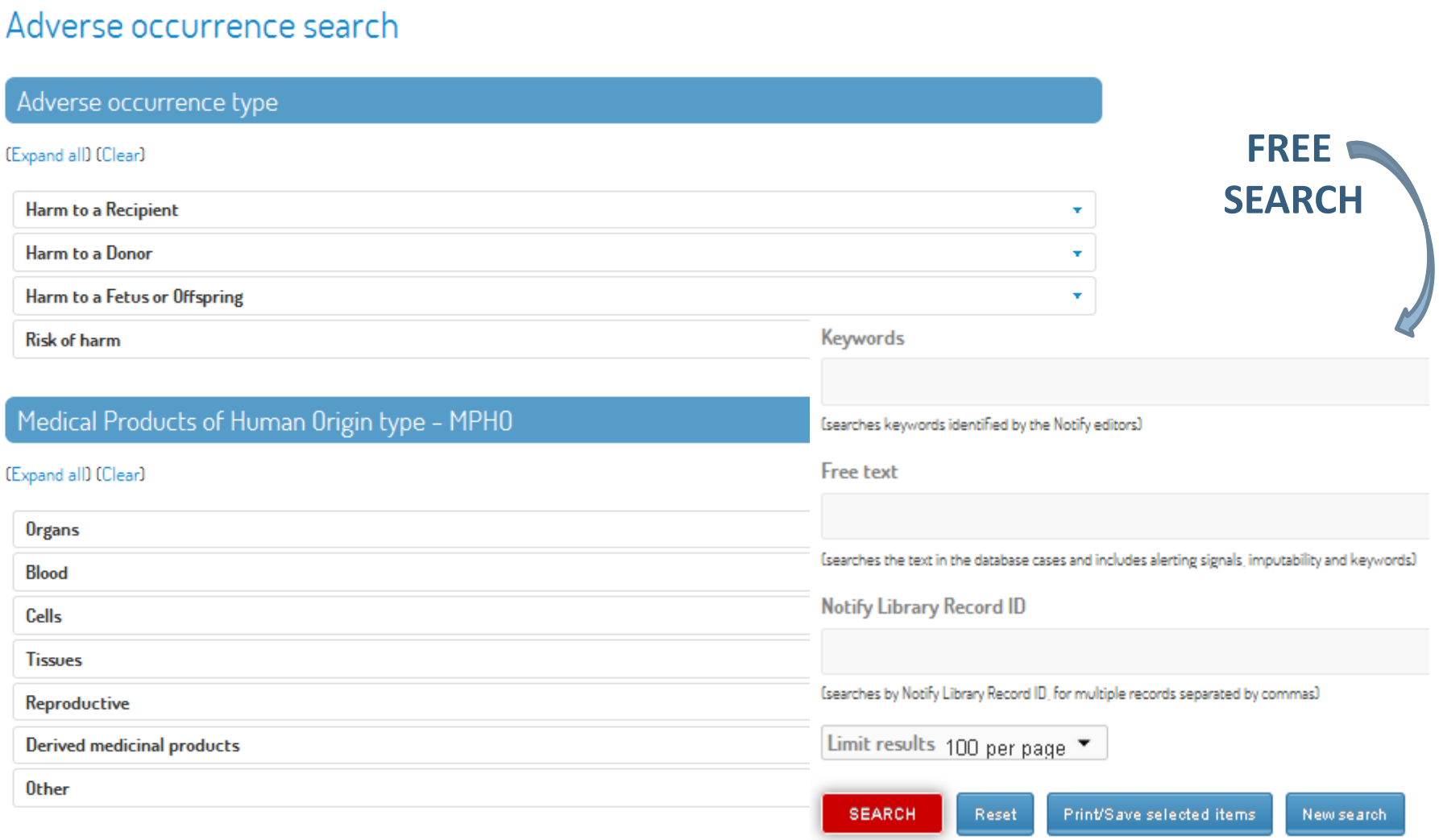
NOTIFY LIBRARY: SEARCH PAGE



NOTIFYLIBRARY

NOTIFY LIBRARY SEARCH RESULTS (1)

Search criteria:

Adverse occurrence:
Risk of harm >> Other
Medical Product of Human Origin type - MPHO:
Organs >> Kidney
Notify Library Record ID:
1685

[4596] Fritsch, L.; Budde, K.; Rogalla, P.; Turk, I.; Neumayer, H.H.; Loening, S.A.
Successful living related kidney transplantation despite renal angiomyolipoma in situ 1999; 162 (2)

Record ID	Adverse occurrence	
1685	**Adverse occurrence description:** Single case report: Renal Angiomyolipoma **Adverse occurrence type:**Risk of harm => Other **MPHO type:** Organs => Kidney **Time to detection:** Known at transplant. 1 cm mass found in living donor kidney (mother) during evaluation but not resectable due to central location. After a nine months observation period to decrease risk of an underlying malignancy, decision to proceed with transplant was made. Inspection after cold perfusion still revealed no good possibility for ex vivo excision, kidney was implanted without further manipulation. Immediate functioning, recovery without complications. Followup imaging showed no growth with 18 month followup. **Alerting signals, symptoms, evidence of occurrence:** Detected pre-transplant in donor by ultrasound. No complications in recipient. **Estimated frequency:** Not discussed in European Council Guidelines. Frequency estimated at 1-3% of population (Wallace MJ, Wallace S. Renal angiomyolipoma. In: Adam A, Dondelinger RF, Mueller PR, eds. Interventional Radiology in Cancer. New York: Springer-Verlag; 2004:204). **Demonstration of Imputability or Root cause:** Identification in donor kidney prior to transplant. **Imputability grade:** 3 Definite/Certain/Proven **Expert comments for publication:** Angiomyolipoma is considered to be a benign tumor curative by resection. Reports of metastatic spread are rare and controversial; the question of metastases versus multicentricity is not conclusively resolved. However, rare highly atypical angiomyolipomas (highly pleomorphic, necrosis, mitotic activity on histologic examination) raise concern for atypical behavior. The authors note in the current report that a large study (Steiner MS et al., J Urol 150:1782, 1993) showed asymptomatic course for angiomyolipomas <4 cm. In followup discussion of this report (in J Urol 163; 924, 2000) the authors state that they were aware of "at least two other cases of rejection of a kidney allograft with angiomyolipoma" but considered that to be coincidental and noted a more likely risk of bleeding from the tumor which should be considered during decision making. It is estimated that 80% of angiomyolipomas are sporadic and 20% are associated with tuberous sclerosis (Steiner MS, et al. The natural history of renal angiomyolipoma. J Urol. 1993;150:1782-1786). Although considered a benign tumor, uncommon variants exist that are capable of aggressive or malignant behavior (reviewed in https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5644357/) **Keywords:** angiomyolipoma kidney kidney transplant known in donor malignancy case report living donor	1 reference

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NOTIFY LIBRARY SEARCH RESULTS (2)

SEARCH | Reset | Print/Save selected items | Save XLS selected items | Save XLS all items | New search

☐ 2061

Adverse occurrence description: Ureaplasma
Adverse occurrence type: Harm to a Recipient => Infection => Bacterial => Ureaplasma
MPHO type: Organs => Lung
Time to detection: Detection of symptoms occurs within 1-3 days of transplantation
Alerting signals, symptoms, evidence of occurrence: Lung infiltrates, systemic inflammatory response syndrome, altered mental status, hyperammonemia, death within 1-3 days of transplantation. Trend towards greater incidence of grade 3 primary graft dysfunction, acute renal failure, acute rejection and 60 day mortality. Two cases reported of bronchial dehiscence. 100% mortality unless treated with antibiotics (macrolide plus doxycycline or quinolone) although antimicrobial therapy may not be 100% protective. Requires two antibiotics due to risk of resistance.
Estimated frequency: Recognition of Ureaplasma urealyticum as a cause of fatal hyperammonemia in lung recipients within days of transplantation has been reported since 2015. Two subsequent papers reporting donor testing of infected recipients compared to noninfected recipients indicated that all cases of fatal hyperammonemia and Ureaplasma infection occurred in donors and recipients who screened BAL (bronchoalveolar lavage) positive for Ureaplasma, while no cases were found from donors and recipients who screened negative. There is no available estimated frequency, but a paper by Fernandez et al of 29 lung recipients of 28 donors screened all donors for Ureaplasma. 4 donors were positive for Ureaplasma (14%), and their lung recipients all developed hyperammonemia, lung infiltrates and systemic inflammatory response syndrome requiring vasopressors (Fernandez R, Chi M, Ison et al. Am J of Resp and Critical Care Medicine 2017, 195(5)). The literature in this area is limited, but based on this study, indicates a significant transmission frequency (14%).
Demonstration of Imputability or Root cause: Data is based on two reports - one report (Fernandez et al. listed above) of 4 lung donors who tested positive for Ureaplasma (culture/PCR) with pretransplant Ureaplasma negative recipients all resulting in recipients who became Ureaplasma culture/PCR positive and symptomatic. A second paper (also Fernandez et al. J of thoracic surgery 2017) reported on another case of probable donor-derived Ureaplasma parvum (pre-implantation BAL culture and PCR positive; tested retrospectively); the recipient had a negative pretransplant BAL followed by post transplant BAL culture and PCR positivity for Ureaplasma parvum, with clinical and radiological response to dual azithromycin and doxycycline.
Imputability grade: 3 Definite/Certain/Proven
Expert comments for publication: This is an important and relatively newly recognized donor derived infection, particularly in lung recipients; consideration might be given to screening of donor lung BAL and post -transplant recipient testing. Sexually active donors with aspiration pneumonia may represent a risk for Ureaplasma presence in the lower respiratory tract but this is based on the observations from these few reported cases. Ureaplasma infection of the genito-urinary tract is common but it is not part of the normal respiratory tract flora; risk factors for its presence in donor lungs and associated mortality warrant the need for future studies to investigate the optimal strategies for Ureaplasma detection, prophylaxis and treatment. The papers included in this record discuss these issues.
Keywords:

Ureaplasma urealyticum | Ureaplasma parvum | ureaplasma | hyperammonemia | systemic inflammatory response | lung infiltrates | SOT (solid organ transplantation) | lung | lung transplant

3 references

[4862] Fernandez, R.; Chi, M.; Ison, M.G.; Waites, K.B.; Crabb, D.M.; Ratliff, A.E.; Cajigas, H.; DeCamp, M.M.; Odell, D.; Budinger, G.R.; Bharat, A.
Sequelae of Donor-derived Mollicutes Transmission in Lung Recipients 2017; 195 (5) :7

[4861] Fernandez, R.; Ratliff, A.; Crabb, D.; Waites, K.B.; Bharat, A.
Ureaplasma Transmitted From Donor Lungs Is Pathogenic After Lung Transplantation 2017; 103 (2)

[4863] Bharat, A.; Budinger, G.R.Scott; Ison, M.G.
Donor-derived ureaplasma is a potentially lethal infection in lung allograft recipients 2017; 36 (8) :7

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ADVERSE OCCURRENCE TYPE TAXONOMY (extract)

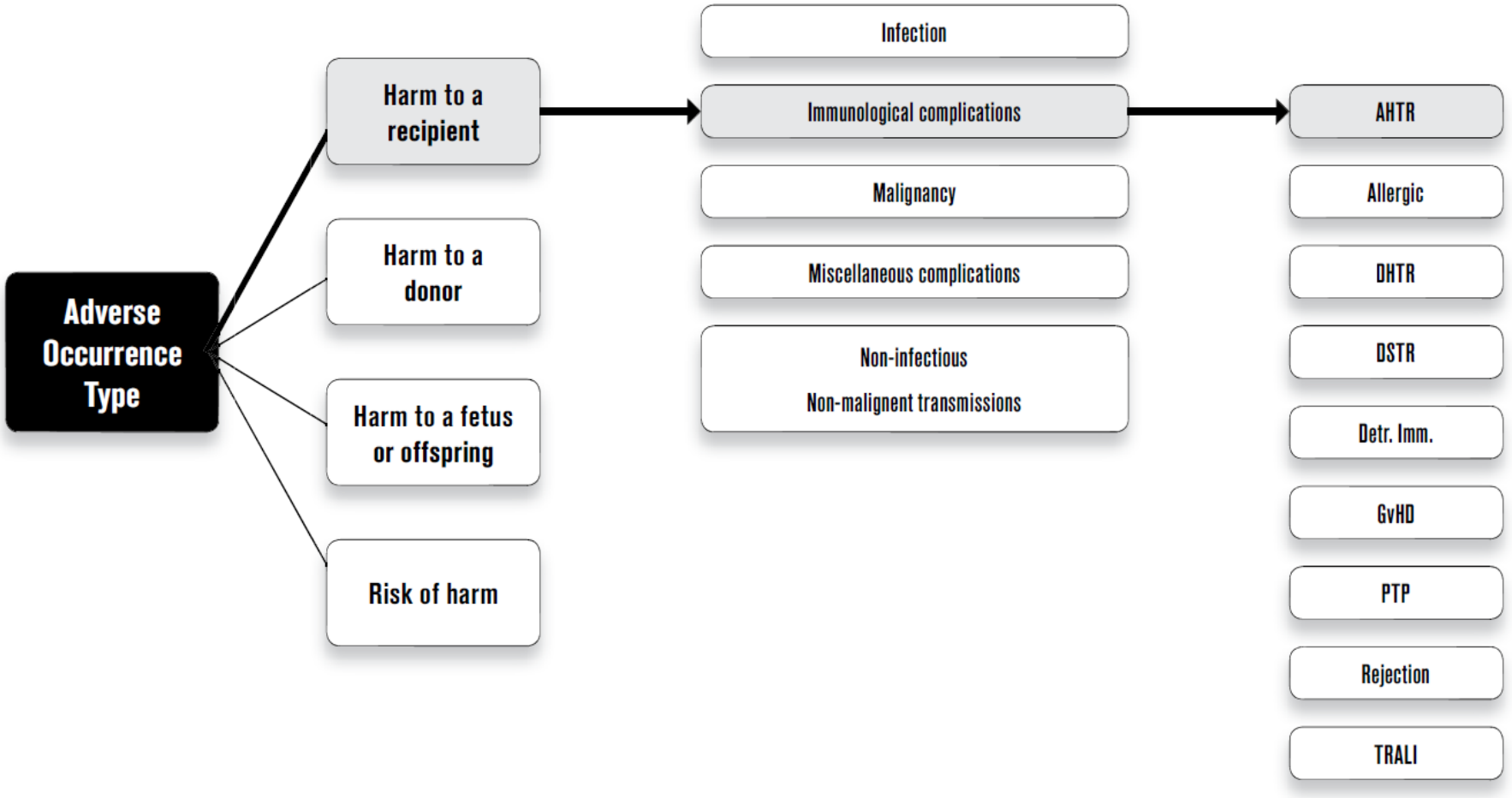
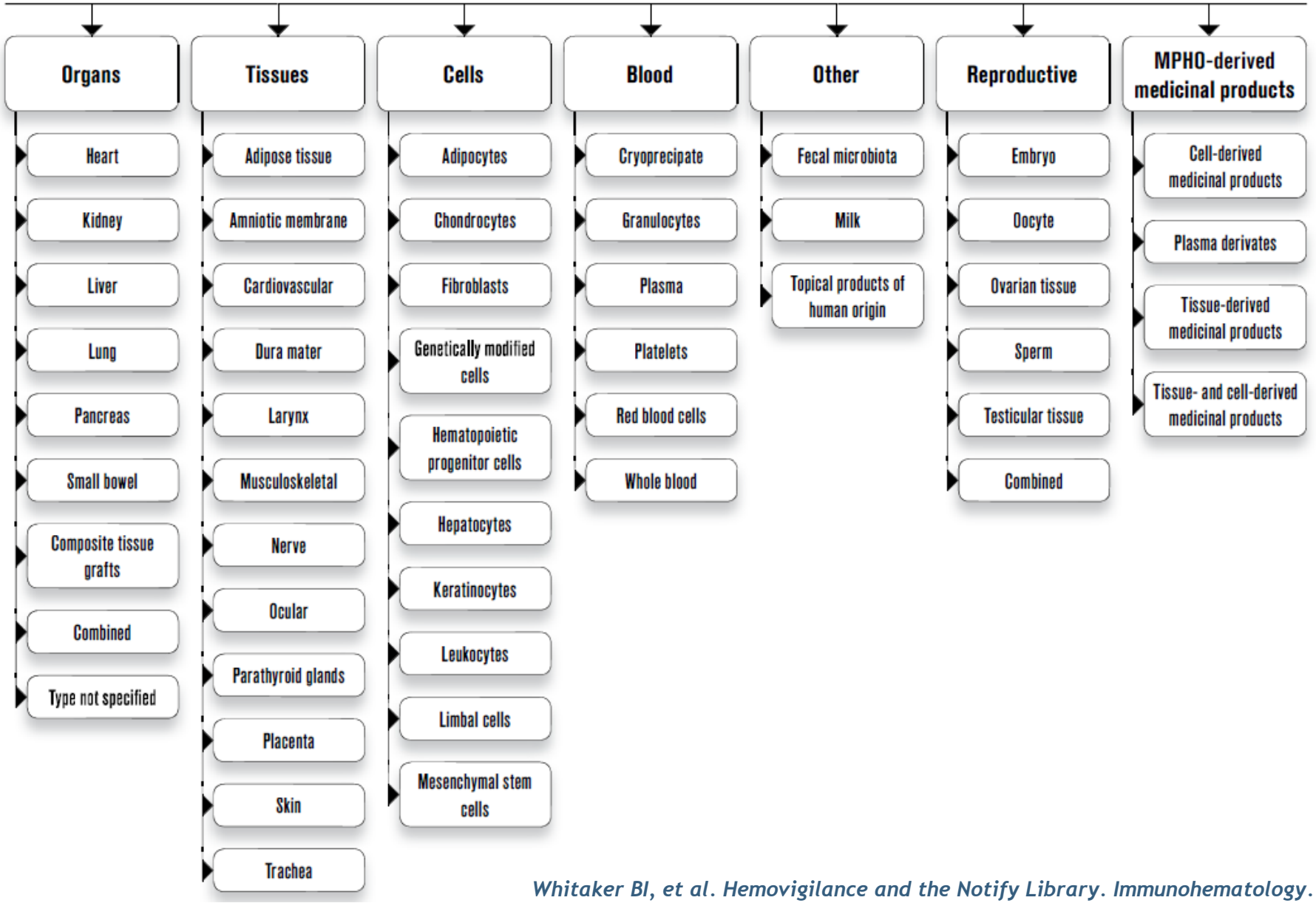


Fig. 1 Adverse occurrence type taxonomy (extract). AHTR = acute hemolytic transfusion reaction; DHTR = delayed hemolytic transfusion reaction; DSTR = delayed serologic transfusion reaction; Detr. Imm. = detrimental immunization; GvHD = graft-versus-host disease; PTP = post-transfusion purpura; TRALI = transfusion-related acute lung injury.

Whitaker BI, et al. Hemovigilance and the Notify Library. Immunohematology. 2017 Dec;33(4):159-164

MPHO TAXONOMY



Whitaker BI, et al. Hemovigilance and the Notify Library. Immunohematology. 2017 Dec;33(4):159-164

FREE TEXT VS STRUCTURED DATABASE SEARCH EXAMPLE

- Free text search: "acute respiratory distress"

293 records

125 records

- Free text search: "acute respiratory distress"
- MPHO: Blood

- Free text search: "acute respiratory distress"
- MPHO: Blood → Platelets

29 records

IMPUTABILITY TABLE

TABLE 1.
Imputability table used for the assessment of cause and effect for each Notify record

Imputability Grade	Criteria for infectious and malignant transmissions adapted from DTAC[8]	Adapted from EUSTITE—SOHO V&S[9] and proposed standard definitions for surveillance of noninfectious adverse transfusion reactions[10]	Adapted from EUSTITE—SOHO V&S in assisted reproductive tecnologies[9]
Not assessable	Insufficient data for imputability assessment	Insufficient data for imputability assessment	Insufficient data for imputability assessment
Excluded	Suspected transmission and fulfillment of at least one of the following conditions: - Clear evidence of an alternative cause. - The appropriate diagnostic tests performed have failed to document infection by the same pathogen in any recipient from the same donor. Laboratory evidence that the recipient was infected with the same pathogen or had a tumor before the application of organs, tissues, or cells.	Conclusive evidence beyond a reasonable doubt that the adverse occurrence can be attributed to causes other than the transfusion of blood components or transplantation of tissues/cells	Conclusive evidence beyond reasonable doubt for attributing to alternative causes than the ART process
Possible	Suspected transmission and: - Laboratory evidence of the pathogen or tumor in a single recipient, *or* Suspected transmission and: - Laboratory evidence of the pathogen or tumor in a single recipient or - Data suggest a transmission but are insufficient to confirm it.	The evidence is indeterminate for attributing the adverse occurrence either to the quality/safety of tissues/cells/blood components (for recipients), to the donation process (for donors), or to alternative causes	Evidence is indeterminate
Likely/probable	The following 2 conditions are met: - Suspected transmission. - Laboratory evidence of the pathogen or the tumor in a recipient. And it meets at least one of the following conditions: - Laboratory evidence of the same pathogen or tumor in other recipients. - Laboratory evidence of the same pathogen or tumor in the donor. If there is pretransplant laboratory evidence, such evidence must indicate that the same recipient was negative for the pathogen involved before transplantation.	The evidence is clearly in favor of attributing the adverse occurrence to the quality/safety of tissues/cells/blood components (for recipients) or to the donation process (for donors)	The evidence is in favor of attributing to the ART process
Definite/certain; proven	All the following conditions are met: - Suspected transmission. - Laboratory evidence of the pathogen or the tumor in a recipient. - Laboratory evidence of the same pathogen or tumor in other recipients (if multiple recipients). - Laboratory evidence of the same pathogen or tumor in the donor. - If there is pretransplant laboratory evidence, then it should be noted that the same recipient was negative for the pathogen before transplantation.	The evidence is conclusive beyond reasonable doubt for attributing the adverse occurrence to the quality/safety of tissues/cells/blood components (for recipients) or to the donation process (for donors)	Conclusive evidence beyond reasonable doubt for attributing to the ART process

ART, assisted reproduction technologies; DTAC, Disease Transmission Advisory Committee; EUSTITE, European Union Standards and Training for the Inspection of Tissue Establishments Project (GA 2005204); SOHO V&S, Vigilance and Surveillance of Substances of Human Origin Project (GA 20091110).

For each Record are described:

- Latency
- Estimated frequency
- Signs
- Symptoms
- How the adverse event was detected
- The method used to assess imputability

Based on the information in the reference or V&S report, imputability is categorized:

- Proven
- Probable
- Possible
- Unlikely
- Excluded

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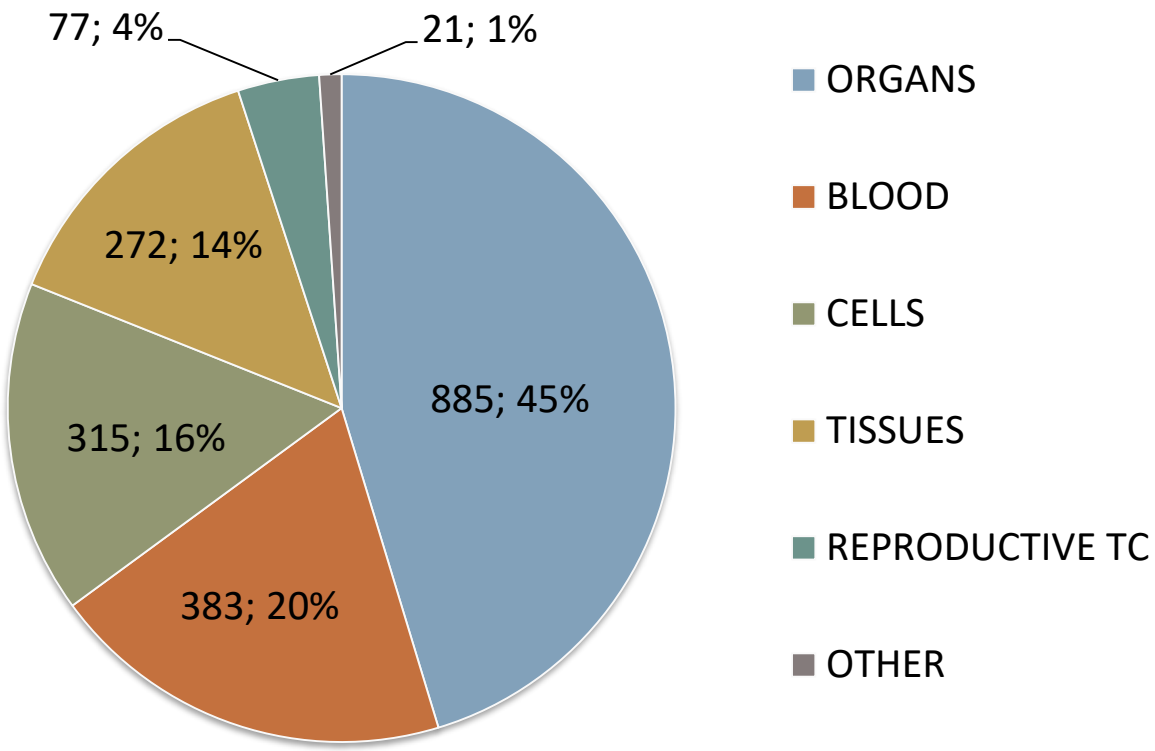
NOTIFY LIBRARY'S CONTENT BY MPHO TYPE

1,953 Notify records

2,860 references indexed



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CONTENT ANALYSIS BY MPHO TYPE

	ORGANS n. (%)	TISSUES n. (%)	BLOOD n. (%)	CELLS n. (%)	REPRODUCTIVE TC n. (%)	OTHER n. (%)
	Kidney 371 (42%)	Musculoskeletal 117 (43%)	Red blood cells 213 (56%)	HPC 304 (96.5%)	Sperm 31 (41%)	Plasma derivates 14 (67%)
	Liver 267 (30%)	Ocular 101 (37%)	Platelets 79 (21%)	T-lymphocytes 4 (1.3%)	Embryo 27 (36%)	Placenta 1 (4,5%)
	Lung 80 (9%)	Cardiovascular 27 (10%)	Plasma 43 (11%)	Chondrocytes 2 (0.6%)	Oocyte 15 (20%)	Milk 5 (24%)
	Heart 57 (6%)	Dura mater 11 (4%)	Whole blood 27 (7%)	Pancreatic Islets 2 (0.6%)	Ovarian tissue 2 (3%)	Topical products of human origin 1 (4,5%)
	Multiple or type not specified 54 (6%)	Skin 10 (4%)	Type not specified 17 (4%)	Dendritic cells 1 (0.3%)	Combined 1 (1%)	
	Combined 27 (3%)	Amniotic Membrane 3 (1%)	Granulocytes 4 (1%)	Mesenchymal stem cells 1 (0.3%)		
	Pancreas 15 (2%)	Adipose tissue 2 (0.7%)		Olfactory mucosal cells 1 (0.3%)		
	Composite tissue grafts 9 (1%)	Nerve 1 (0.3%)				
	Small bowel 5 (1%)					
TOTAL	**885 (45%)**	**272 (14%)**	**383 (20%)**	**315 (16%)**	**77 (4%)**	**21 (2%)**

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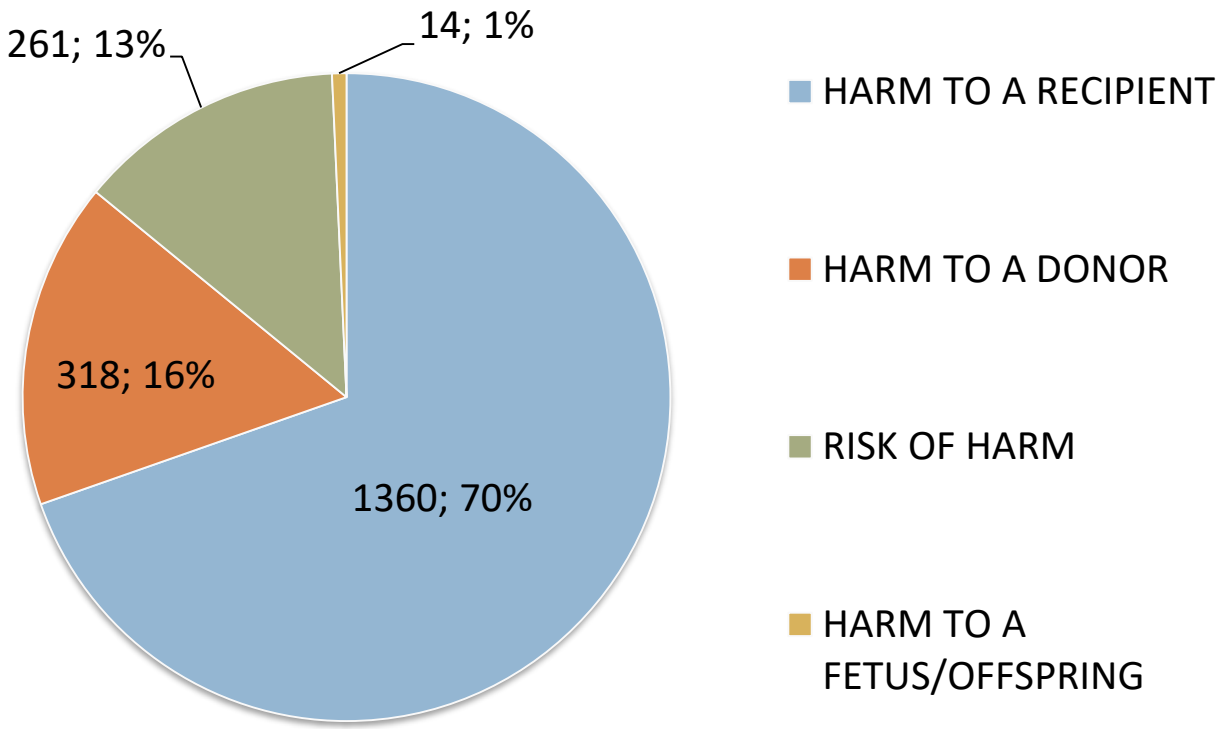
NOTIFY LIBRARY'S CONTENT BY ADVERSE OCCURRENCE TYPE

1,953 Notify records

2,860 references indexed



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HARM TO A RECIPIENT

Harm to a recipient (%)	Organs	Tissues	Blood	Cells	Reproductive TC	Other	Total
Infection transmission (47%)	341	129	116	36	9	5	636
Malignancy transmission (26%)	324	6	0	28	0	0	358
Immunological complications (15%)	20	7	153	14	2	11	207
Miscellaneous complications (8%)	4	20	55	34	0	1	114
Non infectious, non malignant transmission (4%)	13	0	6	26	0	0	45
Total	702	162	330	138	11	17	1360

HARM TO A DONOR

Harm to a donor	Organs	Tissues	Blood	Cells	Reproductive TC	Other	Total
Allergic reactions	0	0	3	1	0	0	4
Drug related reactions	0	0	0	50	2	0	52
Embolic complications	6	0	2	7	0	0	15
Excessive collection/removal	0	0	4	0	0	0	4
Infection	13	3	0	10	2	0	28
Malignancy	0	0	0	3	0	0	3
Toxicity	0	0	2	2	0	0	4
Miscellaneous complications	77	15	16	54	1	0	163
Vasovagal reactions	0	0	12	9	0	0	21
Other	6	0	3	14	1	0	24
Total	102	18	42	150	6	0	318

RISK OF HARM

Risk of harm	Organs	Tissues	Blood	Cells	Reproductive TC	Other	Total
Loss of a suitable MPHO	20	33	1	19	33	0	106
Mix-up	1	0	0	1	8	0	10
Unsuitable MPHO released for clinical use	6	51	3	3	5	4	72
Donor disease without transmission	48	3	0	1	0	0	52
Other	6	5	7	3	0	0	21
Total	81	92	11	27	46	4	261

Last update: September 3, 2024

Official Journal of
The Transplantation Society &
International Liver Transplantation Society

Transplantation®

September 2021 - Volume 105 – Number 9

Jeremy Chapman *Donor-derived Disease—Who to Notify? doi: 10.1097/TP.0000000000003590*

Petrisli E; Carella C; Navarro A; Fehily D; Strong DM; Cardillo M; on behalf of the Notify Editorial Board. *Vigilance for Medical Products of Human Origin—Progress on the Notify Library's Global Effort to Share Information and Learning,* Transplantation: 2021;105(9):1921-1929 doi: 10.1097/TP.0000000000003589

NEW!!

Alteri A, Petrisli E, Nolan P, Pisaturo V, Fehily D, Navarro A, Strong DM, Cardillo M, Costa M. *Learning from incidents in medically assisted reproduction: the Notify Library as a learning tool.* Reprod Biomed Online. 2021 Oct;43(4):581-585. doi: 10.1016/j.rbmo.2021.07.015. Epub 2021 Jul 28. PMID: 34465527.

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Thank you for your attention

‘*The only source of knowledge is experience*’

Albert Einstein